Amniotic Fluid Cardiac Troponin T in Pathological Pregnancies with Evidence of Chronic Fetal Hypoxia

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Aim To determine if prenatally measured cardiac troponin T in the amniotic fluid (Am-TnT) could be used as a marker of fetal myocardial hypoxia and necrosis in pathological pregnancy characterized by increased concentration of amniotic fluid erythropoietin (Am-EPO) as a sign of chronic fetal hypoxia.

Method We measured Am-TnT and Am-EPO in 29 pathological and 5 uncomplicated pregnancies. Samples of amniotic fluid were collected prospectively during elective amniocentesis (n = 15), cesarean sections (n = 17), and before elective induction of labor in two pregnancies with stillbirth. Am-TnT and Am-EPO were determined by chemiluminescent immunological method.

Results Am-TnT was undetectable in normal pregnancies, but it was detectable in 9 of 29 amniotic fluid samples from pathological pregnancies, with a median value of 0.030 µg/L (range, 0.010–111.6 µg/L). Am-EPO values were above normal values (>11 U/L) in all pathological pregnancies. Am-EPO concentration showed positive correlation with the Am-TnT concentration (r = 0.526, P = 0.003). Median concentration of Am-EPO in 9 pregnancies with detectable Am-TnT was 198 U/L (range, 16-3,378 U/L). In 20 pathologic pregnancies with undetectable Am-TnT, the median concentration of Am-EPO was 39 U/L (range, 12-293 U/L). There was no statistically significant difference between the groups (P = 0.051).

Conclusion Am-TnT is measurable in some pathological pregnancies with signs of fetal chronic hypoxia and myocardial involvement and could be potentially used as a biochemical marker of fetal myocardial injury.

Perinatal asphyxia may be associated with fetal cardiac dysfunction due to myocardial dysfunction (1,2). In neonates, asphyxia may lead to ischemic myocardial damage and, in some cases, to subendocardial infarction (3-8).

Under the conditions of chronic hypoxia, fetus responds by blood flow redistribution to vital organs, such as the brain and the heart. The redistribution of blood flow to the heart (fetal "heart sparing" effect) detected by assessment of coronary blood flow is a further ominous sign of fetal compromise during chronic hypoxia (9,10).

In adults, cardiac troponin T (TnT), the structural protein that binds the troponin complex to the tropomyosin molecular strand, has been proposed as a specific biochemical marker of myocardial infarction and some other conditions with cardiac involvement (11-14). Cardiac TnT seems to be an ideal marker of myocardial hypoxia and necrosis because of its cardiac tissue specificity, and large time window for its detection after a cardiac event. Fetal myocardial damage during pregnancy and/or delivery can be demonstrated in the early neonatal period by high serum TnT concentration, which correlates with the degree of as-

phyxia (15,16). However, there are no clear-cut biochemical markers that would allow early identification of neonates at risk of brain damage or posthypoxic heart failure.

Severe intrauterine growth restriction is often associated with cardiovascular abnormalities detectable by fetal echocardiography (17,18). Increased concentration of erythropoietin in amniotic fluid (Am-EPO >11 U/L) indicates chronic fetal hypoxia of any origin (19).

Type 1 diabetes may lead to macrosomia and fetal organomegalia with consequent ventricular hypertrophy and thickening of the interventricular septum. The three pathological processes implicated as possible causes of fetal compromise in diabetic pregnancies are fetal hypoxia, fetal acidemia, and abnormalities of maternal and/or fetal metabolism. The severity of fetal diabetic cardiomyopathy can vary from undetectable (an incidental finding on echocardiography) to severe symptoms of congestive heart failure (20,21). Hypertrophic cardiomyopathy may explain otherwise unexplained fetal deaths in women with diabetes (22). Other risk pregnancies with fetal cardiac involvement are those with serious intrauterine growth retardation (IUGR) and fetal hydrops of different etiology with cardiac failure.

Our aim was to determine if prenatal cardiac Am-TnT in the amniotic fluid could be used as a biochemical marker of fetal myocardial compromise.

Patients and Methods

Patients

The study group consisted of 29 women with pathological pregnancy including 3 stillbirths, 2 cases of RhD and anti-Kell isoimmunization, 2 cases of fetal hydrops, 7 singleton pregnancies with intrauterine growth restriction (IUGR) estimated as fetal weight below 10th percentile, 2 twin pregnancies with IUGR of either fetus, and 13 pregnancies with fetal macrosomia due to type 1 diabetes in mothers.

Five women with uneventful term pregnancies delivered by elective cesarean section served as a control group. Macrosomia was defined as a birth weight more than 2 standard deviation (SD) units above and IUGR more than 2SD below the mean value of the reference population.

Collection of Amniotic Fluid Samples

The samples of the amniotic fluid were collected during clinically indicated amniocentesis in all diabetic pregnancies for the determination of the fetal lung maturity and Am-EPO concentration. In pregnancies with stillbirth, amniotic fluid samples were collected during cesarean section in one case and before elective induction of labor in two other cases. Amniotic fluid samples from pregnancies with hydrops due to RhD and anti-Kell incompatibility were collected during the first intrauterine red blood cell transfusion. In singleton and twin pregnancies with IUGR and pathological Doppler patterns (absent and/or reversed end-diastolic flow in the umbilical artery), samples were obtained mainly during the clinically indicated amniocentesis for the determination of Am-EPO (a standard procedure in our hospital). In such cases, Am- EPO is an additional parameter in the evaluation of fetal well-being with a good negative predictive value for chronic fetal hypoxia. On the other hand, some samples were collected during the caesarean section due to fetal distress confirmed by cardiotocography or/and low biophysical score. The investigators were unaware of the Am-TnT results until the end of the study.

Control samples were obtained at elective cesarean sections in 5 uncomplicated pregnancies (two breech presentations and three repeated cesarean sections). The women were healthy and had healthy newborns with normal birth weight. Samples were taken atraumatically when entering the amniotic sac. None of the samples contained blood or meconium.

The local Ethics Committee approved the study protocol and subjects gave informed consent before the samples of amniotic fluid were taken.

Amniotic Fluid EPO and TnT Measurement

Fresh samples were analyzed immediately in the hospital laboratory. The determination of the Am-EPO was conducted by a chemiluminescent immunological method (Immulite EPO Assay; Diagnostic Products, Los Angeles, CA, USA). Am-TnT analysis was performed by chemiluminescent method with the lowest detection rate of 0.010 μg/L (Elecsys, Roche Diagnostics, Geneva, Switzerland).

Statistical Analysis

The results are presented as median and range. Continuous variables were compared by analysis of variance. Spearman's correlation coefficients were calculated to examine bivariate relationship. $P < 0.05$ was considered statistically significant. SPSS statistical package SPSS Inc. Chicago, IL, USA, version 13.0, 2005) was used for data analysis.

Results

Am-TnT was not detectable in any of the amniotic fluid samples in the control group. Am-EPO was normal (≤11 U/L) in all amniotic fluid samples from normal pregnancies, as expected. Am-TnT was detectable in 9 of 29 amniotic fluid samples from pathological pregnancies, ranging from 0.01 μg/ L to 111.6 μg/ L (median, 0.03 μg/L; Table 1). Am-EPO was above normal range in all pathologic pregnancies (>11 U/L).

Median concentration of Am-EPO in 9 pregnancies with detectable Am-TnT was 198 U/L (range, 16-3,378 U/L). In 20 pathologic pregnancies with undetectable Am-TnT, the median concentration of Am-EPO was 39 U/L (range, 12-293 U/L). The difference between the groups was of borderline significance ($P = 0.051$). Am-EPO concentration showed positive correlation with Am-TnT concentration considering all 29 pathological pregnancies (r = 0.526, $P = 0.003$).

Discussion

In our study, Am-TnT was present in a smaller proportion of pathological pregnancies with specific fetal cardiac pathology and signs of fetal chronic hypoxia characterized by increased Am-EPO, whereas it was undetectable in normal pregnancies.

Ischemia and myocardial necrosis occur in up to 25-51% of newborns with perinatal as-

Table 1. Clinical data on pathological pregnancies with detectable amniotic fluid cardiac troponin T*

Pregnancy outcome	gestational age at birth (weeks)	clinical features	birth weight (g)	Apgar score	uapH	Am-EPO (U/L)	Am-TnT (μg/L)	Comment
			Characteristics of newborns					
Stillbirth:								
case 1	26+2	fetal intrauterine demise with asymmetric IUGR, oligohydramnios	550	0		215	0.238	normal karyotype, no anomalies
case 2	35+0	fetal macrosomia with interventricular septal thickness 1.3 cm	4,030	0		56	111.6	4 days prior to demise normal bioprofile, cardiotocogram and Doppler
Fetal hydrops:								
case 3	31+5	unexplained hydrops with heart failure	2,260	1	6.75	3,378	0.013	emergency cesarean section due to poor bioprofile and cardiotocogram, exitus on the third postnatal day
case 4	32+5	hydrops with heart failure due to Rh (D) isoimmunization	2,332	6	7.34	198	0.435	2 intrauterine red blood cell transfusions, maternal drug addiction and poor compliance, pulmonary hypertension and 4 exsanguinotransfusions, neurodevelopmental outcome normal
case 5	42+2	hydrops and heart failure at gestational age 23+0 due to parvo-virus infection	4,130	9	7.34	154	0.180	4 intrauterine blood cell transfusions, resolution of hydrops at gestational age 28+0, normal vaginal birth with vigorous healthy newborn
IUGR (singleton pregnancy):								
case 6	28+4	IUGR, umbilical artery and ductus venosus reverse flow	840	8	7.17	490	0.026	prenatal exposure to buprenorphine, fetal tetralogy of Fallot, postnatal cardiac surgery, periventricular leukomalacia, died due to hemorrhage from bronchomalacia
case 7	29+1	IUGR, umbilical artery and ductus venosus reverse flow	410	7	7.33	221	0.014	early neonatal death due to extreme prematurity
IUGR (twin pregnancy):								
case 8	28+0	twin A-oligohydramnios, brain sparing, IUGR and umbilical artery reverse flow	700	7	7.16	151	0.030	dichorionic twins, unremarkable postnatal development
case 9	32+0	twin B-umbilical artery reverse flow, poor cardiotocogram	1,455	8	7.30	16	0.010	monochorionic twins, unremarkable postnatal development

*Abbreviations: uapH – umbilical artery pH; Am-EPO – amniotic fluid erythropoietin; Am-TnT– amniotic fluid cardiac troponin; IUGR – intrauterine growth restriction.

phyxia (1). When continuation of pregnancy could jeopardize the fetus, the time of delivery must be optimized. Fetuses with IUGR are the most vulnerable to prenatal hypoxia and the clear criteria for the optimal time of delivery of these fetuses are still missing (23,24).

There are many non-invasive methods of fetal prenatal surveillance, but none of them have yet been proven to be superior to others. Invasive methods, such as prenatal umbilical blood sampling, are nowadays almost abandoned, though amniotic fluid sampling and measuring of certain markers of fetal hypoxia, such as erythropoietin (25,26), endothelin-1 (26), and myoglobin (27), may be useful. Of all amniotic fluid markers, erythropoietin has been the most intensely investigated.

There is ample evidence of fetal cardiac dysfunction in certain high-risk pregnancies (17, 18). In some fetuses with severe IUGR, increased right ventricular afterload and coronary blood flow can be observed (9,10). These fetuses can sustain subclinical myocardial injury, which may be impossible to detect by conventional methods of fetal surveillance. They may also be predisposed to myocardial infarction in adult life (28). Thus, we need more sophisticated methods of early detection of fetal myocardial damage.

During intrauterine development, a fetal isoform of cardiac troponin T (cTnT) is expressed transiently in skeletal muscles (down-regulated in adult skeletal muscles). In our study, such isoforms were not detected by the Elecsys M7 and M11.7 antibody pair of the Roche diagnostic cTnT assay (12).

Fetal myocardial cell damage was detectable in several studies that found the increased concentration of the cardiac troponin(s) in the cord blood or samples obtained in early neonatal period as a marker (2,16,28,29). These studies determined TnT in either the umbilical blood or postnatally at different intervals and used different reference values, so their results cannot be compared. Some studies used cardiac troponin I as a marker of the fetal myocardial damage (28-32). Furthermore, umbilical blood is very vulnerable to hemolysis, which can also affect the results.

We show here for the first time that Am-TnT may be detectable in certain high-risk pregnancies with possible fetal myocardial damage. It is unclear why some IUGR fetuses have a myocardial injury and others do not, despite the similar pattern of very severe placental insufficiency with absence or reversal of end diastolic flow and pathological Doppler on the venous side. In the majority of fetuses with severe IUGR, sequential deterioration of arterial and venous flows precedes deterioration of biophysical profile score (10,17,18,34).

There are only a few studies in which both the umbilical TnT concentrations and fetal (neonatal) hemodynamic assessment were simultaneously used to determine their usefulness in the diagnosis of heart damage (2,34).

In our study, severe arterial and venous pathological changes were found by Doppler in cases No. 6-9. In these cases, severe placental insufficiency was present with consecutive fetal IUGR and signs of distress confirmed by ultrasound, cardiotocography, and biochemical markers of chronic fetal hypoxia. Other fetuses with IUGR but undetectable Am-TnT concentration had milder forms of placental insufficiency (umbilical artery absence or reversal of end diastolic flow without compromise on the venous side). We speculate that in severe forms of placental insufficiency, it might be wiser to deliver fetuses before the fatal preterminal signs of hemodynamic deterioration occur. Doppler evaluation seems to be more sensitive than cardiotocography in making delivery decision in certain cases (23).

Fetal cardiac failure and the consequent myocardial damage can be caused by hydrops or myocarditis of viral origin. In our study, cases No. 3-5 had hydrops with heart failure and detectable concentration of Am-TnT. Fortunately, it seemed that heart failure and suspected myocardial damage were reversible, as observed in case No. 5, where a healthy infant was delivered 14 weeks after the first appearance of signs of hydrops and heart failure due to anemia caused by parvovirus infection. Other anemic fetuses without hydrops and heart failure had undetectable Am-TNT.

Women with type 1 diabetes still have a five-fold risk of stillbirth compared with women with normal pregnancies (35). In diabetic pregnancies, a normal results of non-stress test does not exclude intrauterine death, which may occur within a few days after the test. This implies that di-

abetic pregnancies should be under intensive surveillance, especially after 34 week of gestation.

In our case No. 2, four days before intrauterine fetal demise, normal reactive cardiotocogram and unremarkable Doppler status and fetal biophysical profile were observed. At that time, fetal cardiac septal thickness was 13 mm. It is known that fetal transient hypertrophic cardiomyopathy complicates up to 30% of diabetic pregnancies (25,36). The amniotic fluid from pregnancy in case No. 2 contained extremely high concentrations of TnT, which was measured twice to exclude laboratory error. Troponin concentration in maternal plasma was normal. This is in agreement with the previous findings, where no correlation between maternal and umbilical (fetal) troponin concentrations was established. This may suggest that there is no passage of cardiac TnT either from the fetus to the mother or from mother to the fetus (37). We speculate that the fetus might have died of myocardial damage due to hypertrophic cardiomyopathy and subsequent cardiac failure. We still do not have an explanation for the extremely high Am-TnT values. Chronic hypoxia and possible long-lasting leakage of the TnT from the damaged myocardium and its accumulation might be the reasons. The interesting fact is that concentrations of creatine kinase (CK-MB) and lactic dehydrogenase (LDH) in the amniotic fluid were also very high (Am-CK-MB, 66 µg/L; Am-LDH, 975 U/L), whereas maternal concentrations of the same enzymes were normal. As there are no reference values for those enzymes in the amniotic fluid, the significance of these observations is unknown. Microscopic examination of the fetal heart did not reveal typical signs of myocardial necrosis, but it is well known that fetal tissues show different features in many cases. However, several studies have contradicted a previous assumption that perinatal myocardial infarction is a rare event (4-8). It is uncertain how commonly it does occur, because a very recent infarction is difficult to diagnose by standard histological methods, and early histological changes in the neonate, particularly inflammatory infiltration, may be less remarkable than those seen in the adult. Histological diagnosis of myocardial infarction in stillborns can be difficult because of autolysis (5).

In conclusion, we do not believe that Am-TnT determination could yet be used as a part of routine evaluation of fetal well-being. It requires amniocentesis, which is an invasive procedure requiring a trained specialist and carries a risk of premature rupture of membranes or/and iatrogenic chorioamnionitis. Furthermore, we still do not know enough about the turnover of cardiac TnT in the amniotic fluid, although serial amniocenteses could provide the answer. As 75% of amniotic fluid is fetal urine, it may be possible that the restricted tubular resorption as a result of the tubular ischemic damage may lead to the appearance of TnT in the amniotic fluid. The similar cause of appearance of TnT and TnI in the urine of the adults with acute myocardial infarction with the renal damage was proposed by Ziebig et al (38). Most importantly, it is uncertain whether the very specific and detailed fetal echocardiography is sensitive enough to detect subclinical, but still important, myocardial damage.

The strength of this study is that cardiac TnT was found for the first time in the amniotic fluid samples from some pathological pregnancies, all of which had specific cardiac pathology. Am-EPO concentration was higher in pregnancies in which amniotic fluid cardiac TnT was detectable. We speculate that duration of chronic hypoxia was an important factor in determination of the degree of myocardial involvement.

This study has several limitations. The control group was very small, but as the cardiac TnT was undetectable in all of the analyzed amniotic fluid samples, we considered the sample size to be large enough. The study group was selected on the basis of increased Am-EPO in all pathological pregnancies. There was neither echocardiographic evaluation of fetuses, nor systematic sampling of cardiac TnT from umbilical cord. The clinical significance of the biochemical marker of the fetal myocardial cell damage *in utero* requires further prospective and well-designed studies including larger number of women.

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