

Troponin T and Pro-B-Type Natriuretic Peptide in Fetuses of Type 1 Diabetic Mothers

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OBJECTIVE—Cardiomyopathy is noted in up to 40% of infants of diabetic mothers, and the exact mechanisms are unknown. The aim of this study was to determine whether fetal serum markers of cardiac function differ between normal and type 1 diabetic pregnancies and to examine the relationship between these markers and fetal cardiac structure and function.

RESEARCH DESIGN AND METHODS—This was a prospective observational study of 45 type 1 diabetic pregnancies and 39 normal pregnancies. All participants had concentrations of fetal pro-B-type natriuretic peptide (proBNP) and troponin-T (TnT) measured at the time of delivery. All patients with type 1 diabetes had Doppler evaluation of the umbilical artery, middle cerebral artery, and ductus venosus in the third trimester, and a subset ($n = 21$) had detailed fetal echocardiograms performed in each trimester.

RESULTS—Fetal proBNP and TnT concentrations were higher in the diabetic cohort than in the normal cohort ($P < 0.05$). ProBNP correlated positively with interventricular septum thickness ($P < 0.05$) but not with cardiac function indexes in the third trimester. In patients with poor glycemic control, there was a significant positive correlation ($P < 0.05$) between fetal TnT and the third trimester umbilical artery pulsatility index. There were also increased levels of fetal TnT in infants with poor perinatal outcome ($P < 0.05$).

CONCLUSIONS—Biochemical markers of cardiac dysfunction are elevated in infants of diabetic mothers, especially those with cardiomyopathy or poor perinatal outcome. Hyperglycemia in early pregnancy may affect myocardial and placental development, thus contributing to the susceptibility to hypoxia seen in these infants.

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Pregestational insulin-dependant diabetes (type 1 diabetes) is a relatively common condition in pregnancy, affecting up to 0.5% of the pregnant population (1). Fetuses of diabetic mothers are at increased risk of perinatal morbidity and mortality (2,3). A well-recognized complication of diabetic pregnancy is the condition of hypertrophic cardiomyopathy, which is found in 40% of infants born to diabetic mothers and causes symptoms in 5% (3,4). Whereas diabetic cardiomyopathy is often transient with no lasting consequences for the majority of infants,

impaired cardiac function leading to congestive cardiac failure has been reported in some infants of mothers with poorly controlled diabetes (5). In addition there are case reports of fetal death due to hypertrophic cardiomyopathy (6). Our group has reported previously that stillborn infants of diabetic mothers have heavier hearts than stillborn infants of nondiabetic mothers after correction for fetal size, suggesting that cardiomyopathy may have a role in “unexplained” fetal death in diabetic pregnancy (7). The etiology of this cardiomyopathy is poorly understood with proposed mechanisms

including fetal hyperglycemia, hyperinsulinemia, and chronic hypoxia (8). More recently our group has suggested that cardiomyopathy occurs in response to functional changes evident in the first trimester in fetuses of pregestational type 1 diabetic mothers (9).

Troponin is an inhibitory protein complex found in all striated muscle, and the cardiac-specific isoform troponin T (TnT) is a sensitive and specific marker of myocardial ischemia. The TnT concentration in cord blood is unaffected by gestation, birth weight, sex, or mode of delivery (10). Newborns with intrapartum asphyxia have increased plasma troponin I and TnT concentrations, suggesting that the fetal heart is sensitive to acute hypoxia (11,12). TnT levels are significantly higher in sick neonates who subsequently develop respiratory distress compared with healthy neonates, suggesting that cardiorespiratory compromise in the neonate may be assessed by this biochemical marker (13).

B-type natriuretic peptide (BNP) is a 32-amino acid peptide released by ventricular cardiac myocytes in response to cardiac volume and pressure overload. It exerts a vasodilatory and natriuretic effect and is increased in patients with heart failure, including those with hypertrophic and dilated cardiomyopathy (14). It is initially released as an inactive prohormone (proBNP) that appears to be a sensitive marker for acute cardiac stress (15). Natriuretic peptides also appear to have a role in regulating cardiac growth and may have a cardioprotective role in preventing cardiomyopathy as mice lacking BNP or BNP receptor genes display cardiac fibrosis and hypertrophy (16).

Pregestational type 1 diabetes in the pregnant mother is strongly associated with neonatal cardiomyopathy (odds ratio 15.1 [95% CI 5.5–41.3]) (17). However, there is a paucity of data in the literature on biochemical assessment of fetal cardiac function in pregestational type 1 diabetic pregnancy. There are only two studies in the literature on fetal proBNP in pregestational type 1 diabetic pregnancy (18,19) and none on fetal TnT. The primary aim of this study was to as-

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sess whether fetal cardiac damage, as assessed by cord blood TnT and proBNP levels, differs between normal and type 1 diabetic pregnancy. A secondary aim was to determine whether there is a relationship between these biochemical cardiac markers and glycemic control, fetal cardiac function or structure, placental hemodynamics, or perinatal outcome.

RESEARCH DESIGN AND METHODS

A total of 45 pregestational type 1 diabetic pregnant women and 39 normal nondiabetic pregnant women were included in this prospective observational study. Patients gave informed written consent, and institutional ethics approval was obtained. The National Maternity Hospital has an annual delivery rate of ~9,000 births per annum. The control group consisted of 39 neonates born after uncomplicated pregnancies with no evidence of impaired glucose tolerance. None of these women had glycosuria during their pregnancy or any other indication for formal glucose tolerance testing. A random serum glucose measurement was obtained at the time of recruitment to the study, and this was <7 mmol/l for all control subjects.

This center provides care for 35–40 pregestational type 1 diabetic mothers annually. Patients attend a dedicated multidisciplinary clinic staffed by obstetricians, diabetologists, dietitians, and a midwife specializing in diabetic pregnancies. The first visit in early pregnancy is at ~6 weeks, and patients are usually seen every 2 weeks thereafter. The mean \pm SD duration of diabetes in the diabetic cohort was 16.5 ± 8.7 years. With regard to white class, there were 16 B, 5 C, 15 D, 6 R, and 3 R/F. Eleven women (24%) of our population had vasculopathy, defined as white class R, F, R/F, or the presence of prepregnancy hypertension. Twenty-seven women (60%) delivered a macrosomic infant, defined as birth weight greater than the 90th centile for gestational age and sex based on growth charts (Child Growth Foundation, London, 1996) used in this institution (20). None of the diabetic cohort were smokers; unfortunately, accurate smoking data were not available for the normal cohort.

Glycemic control

Early pregnancy good glycemic control is defined as an A1C value of <7% at the first visit to the multidisciplinary diabetes clinic. Glycemic control is monitored eight times daily by patients, and patients

Table 1—Descriptive data of normal and pregestational diabetic cohorts

| | Normal | Type 1 diabetes | P |
|-------------------------------------|------------------|------------------|-------|
| n | 39 | 45 | |
| Maternal age (years) | 32 \pm 5 | 32 \pm 4 | NS |
| Parity | 1 (0–4) | 1 (0–3) | NS |
| BMI (kg/m ²) | 22.97 \pm 3.57 | 26.13 \pm 4.34 | 0.001 |
| Duration type 1 diabetes (years) | N/A | 16 (1–32) | |
| Vasculopathy | N/A | 11 (24%) | |
| TnT (ng/ml) | 0.00 (0–0.02) | 0.02 (0–0.05) | 0.006 |
| ProBNP (pmol/l) | 86 (6–166) | 126 (0–254) | 0.015 |
| Early pregnancy A1C (%) | N/A | 7.5 \pm 1.5 | |
| 14/40 A1C (%) | N/A | 6.6 \pm 0.9 | |
| 20/40 A1C (%) | N/A | 6.2 \pm 0.8 | |
| 36/40 A1C (%) | N/A | 6.3 \pm 0.8 | |
| Birth weight(g) | 3,568 \pm 486 | 3,805 \pm 416 | 0.018 |
| Birth weight centile | 59.3 \pm 30.5 | 84.4 \pm 17.8 | 0.000 |
| Macrosomia | 12 (31%) | 27 (60%) | 0.008 |
| Gestational age at delivery (weeks) | 39 \pm 1 | 38 \pm 1 | 0.000 |
| Mode of delivery | | | |
| Planned CS | 20 (59%) | 21 (47%) | NS |
| Emergency CS | 7 (18%) | 11 (24%) | NS |
| Vaginal delivery | 12 (31%) | 13 (29%) | NS |
| Apgar score at 1 min | 9 | 9 | NS |
| Apgar score at 5 min | 9 | 9 | NS |
| Cord pH arterial | 7.29 \pm 0.04 | 7.25 \pm 0.08 | 0.016 |
| Venous | 7.35 \pm 0.04 | 7.30 \pm 0.09 | 0.017 |
| Infants born with pH \leq 7.2 | 0 (0%) | 10 (25%) | 0.007 |
| Admission to NICU | 1 (2.6%) | 24 (53%) | 0.000 |
| Poor perinatal outcome | 1 (2.6%) | 17 (38%) | 0.000 |

Data are means \pm SD, median (range), median (interquartile range), n (%), or median. Vasculopathy: white class R, F, R/F, or the presence of pre pregnancy hypertension; early pregnancy A1C: A1C at gestational age 7 \pm 3 weeks; CS, cesarean section; Macrosomia is birth weight greater than the 90th centile for gestational age and sex based on growth charts (Child Growth Foundation, London, 1996).

phone in their results twice per week for advice on insulin dose alteration. Values for fasting and postprandial glucose are considered abnormal if they are >5 and 7 mmol/l, respectively. First, second, and third trimester good glycemic control is defined as an A1C value less than the median for the cohort in that trimester, i.e., first <6.6%, second <6.2%, and third A1C <6.3% (Table 1).

Ultrasonographic measurements

All patients in the diabetic cohort ($n = 45$) had cord blood sampling and Doppler ultrasonographic evaluation of the umbilical artery, middle cerebral artery, and ductus venosus circulation in the third trimester. A subset of fetuses in the diabetic cohort ($n = 21$) underwent a fetal cardiac echocardiogram to assess cardiac function and structure in each trimester. The fetal echocardiograms were performed at 12–14 weeks (first trimester), 20–22 weeks (second trimester), and 34–36 weeks (third trimester) gestation

by a trained research fellow and a maternal fetal medicine specialist as described previously (9).

Cardiac function

Cardiac function was assessed in each trimester. In brief, systolic function was measured by assessing isovolumetric contraction time and diastolic function was measured by assessing the isovolumetric relaxation time and the ratio between passive and active ventricular filling in both ventricles. Global cardiac function was assessed by measuring the myocardial performance index in both ventricles.

Cardiac structure

Cardiac structure was assessed in the second and third trimester because the small size of the 14-week fetal heart precluded measurement in the first trimester. The interventricular septum (IVS) and left and right ventricular free walls were measured as described previously (9).

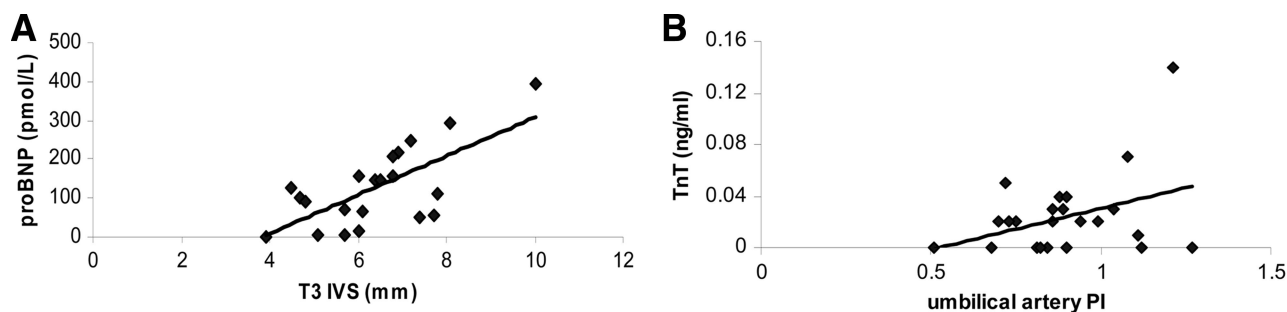


Figure 1—A: Relationship between third trimester (T3) IVS thickness and fetal proBNP. Equation: $y = 49.884x - 191.1$; $R^2 = 0.4753$. B: Relationship between third trimester UAPI and TnT in pregnant women with poorly controlled type 1 diabetes. Poorly controlled type 1 diabetes is defined as early pregnancy A1C $\geq 7\%$ at mean \pm SD gestational age of 7 ± 3 weeks. Equation: $y = 0.0638x - 0.0333$; $R^2 = 0.1418$.

Doppler evaluation

In the third trimester the umbilical artery, middle cerebral artery, and ductus venosus were examined. Fetal cardiac afterload was assessed by obtaining the pulsatility index of the umbilical artery. Cardiac preload was assessed by measurement of the pulsatility index for the ductus venosus. The redistribution of the fetal arterial circulation was assessed by measurement of the pulsatility index of the middle cerebral artery.

Perinatal outcome

A composite “poor perinatal outcome” category was used to divide the type 1 pregestational diabetic cohort into good and poor perinatal outcome. Poor perinatal outcome was defined as one of the following: admission to a neonatal intensive care unit (NICU) for a reason other than hypoglycemia \pm requirement of artificial ventilation; arterial cord pH ≤ 7.2 ; Apgar score at 1 min ≤ 3 ; Apgar score at 5 min < 7 ; or delivery at < 37 weeks. The latter category was included as the four deliveries before 37 weeks in the diabetic population were felt to be related to maternal diabetes: polyhydramnios leading to premature labor ($n = 2$), poor glycemic control and macrosomia ($n = 1$); and preterm prelabor rupture of membranes with emergency caesarean because of meconium grade 2 ($n = 1$).

Biochemical markers

Umbilical blood samples were collected immediately after delivery in serum tubes and centrifuged at 4°C . Serum samples were stored at -20°C until analysis using the Elecsys 2100 (Roche Diagnostics). Plasma proBNP levels were measured via a noncompetitive chemiluminescent assay. The variance was 4.6% (5.6 pmol/l) and 1.9% (107.5 pmol/l), respectively, for low- and high-concentration patient samples, and the respective day-to-day vari-

ance was 5.5% (6.4 pmol/l) and 2.6% (113.6 pmol/l). TnT levels were determined by an electrochemiluminescent sandwich enzyme-linked immunoassay. The minimal detection limit was $0.01 \mu\text{g/l}$ with minimal cross-reactivity with cardiac troponin I (0.002%) and skeletal troponin T (0.001%). The repeatability coefficient for a paired sample was 10%, and the variability coefficient for precision analysis was 6.4%.

Statistical analysis

Statistical analysis was performed with SPSS (version 12). Descriptive statistics and plots were obtained to examine the data and determine distribution, skewness, kurtosis, and outliers. Values > 5 interquartile ranges from the median were excluded from further analysis, leading to the exclusion of three proBNP values and one TnT value.

Statistical analysis was performed by ANOVA when the data were normally distributed with post hoc Bonferroni analysis. Comparisons were made between the two cohorts using the nonparametric Mann-Whitney U test if the data were not normally distributed and Student t test if data were normally distributed. Categorical data were compared using a χ^2 test. A Nonparametric Spearman ρ test and linear regression analysis were used to investigate the relationship between proBNP and TnT and cardiac function and structure parameters and Doppler indexes. $P < 0.05$ was considered statistically significant.

RESULTS

Normal versus diabetic populations

The demographic data of the normal and diabetic populations are summarized in Table 1. The neonates born to pregestational diabetic mothers were delivered

earlier ($P < 0.001$) with a higher birth weight ($P < 0.05$) compared with the control group. There were no differences between the cohorts with respect to mode of delivery or Apgar score at 1 min or at 5 min, but neonates of diabetic mothers were significantly more likely to be admitted to the NICU ($P < 0.001$). Only one of the normal cohort was classified as poor perinatal outcome after spontaneous vaginal delivery with good outcome at 36 weeks. Ten of the diabetic cohort and none of the normal cohort had an arterial pH < 7.2 . Fetal cord blood proBNP and TnT levels were higher in the diabetic cohort ($P < 0.05$), and proBNP correlated positively with TnT ($P < 0.0001$). Neither TnT nor proBNP levels correlated with birth weight centile, gestational age at delivery, or mode of delivery.

Glycemic control

Compared with the normal mothers, pregestational diabetic mothers with good control in early pregnancy had increased cord blood levels of TnT (0.02 ± 0.04 vs. 0.00 ± 0.02 , $P < 0.05$) and similar levels of proBNP (123 ± 137 vs. 86 ± 80 , NS), whereas diabetic mothers with poor control had significantly increased cord blood levels of both TnT and proBNP (0.02 ± 0.07 and 141 ± 78 , respectively). There was no association between proBNP or TnT and first, second, or third trimester maternal glycemic control.

Fetal echocardiography

Cardiac structure. When we divided our diabetic cohort into those with a normal third trimester IVS versus those with a thickened IVS (defined as IVS > 6.39 mm, the mean for the diabetic cohort) we found significantly higher levels of proBNP in those with septal hypertrophy (185 ± 103 vs. 72 ± 54 , $P = 0.008$; $n = 11$ vs. $n = 10$) (Fig. 1A). There was a

Table 2—Effect of advancing gestational age on cardiac function and structural indexes and Doppler indexes in type 1 diabetic pregnancy

| | First trimester | Second trimester | Third trimester |
|-------------------|-----------------|------------------|-----------------|
| Function | | | |
| Left E/A ratio | 0.55 ± 0.05 | 0.62 ± 0.07 | 0.84 ± 0.15 |
| Left IVRT (m/s) | 46 ± 10 | 43 ± 9 | 51 ± 7 |
| Left ICT (m/s) | 38 ± 11 | 36 ± 10 | 34 ± 10 |
| Left MPI | 0.57 ± 0.14 | 0.51 ± 0.11 | 0.57 ± 0.10 |
| Right E/A ratio | 0.61 ± 0.07 | 0.64 ± 0.07 | 0.90 ± 0.32 |
| Right MPI | 0.54 ± 0.12 | 0.53 ± 0.16 | 0.53 ± 0.13 |
| Structure | | | |
| IVS systole (mm) | N/A | 3.24 ± 0.79 | 6.39 ± 1.42 |
| IVS diastole (mm) | N/A | 2.42 ± 0.55 | 5.30 ± 1.32 |
| Right FW (mm) | N/A | 1.74 ± 0.44 | 3.17 ± 0.77 |
| Left FW (mm) | N/A | 1.67 ± 0.42 | 3.15 ± 0.70 |
| UAPI | 1.56 ± 0.45 | 1.19 ± 0.21 | 0.88 ± 0.18 |
| MCAPI | N/A | 1.55 ± 0.30 | 1.58 ± 0.34 |
| DVPI | 0.92 ± 0.44 | 0.76 ± 0.37 | 0.54 ± 0.24 |

Data are means ± SD. DVPI, ductus venosus pulsatility index; E/A ratio, ratio of passive-to-active ventricular filling; FW, free wall of ventricle; ICT, isovolumetric contraction time; IVRT, isovolumetric relaxation time; MCAPI: middle cerebral artery pulsatility index; MPI, myocardial performance index; N/A, not applicable.

significant positive correlation between proBNP and third trimester IVS thickness in both systole and in diastole (r coefficient 0.489, $P < 0.05$). There was no significant correlation between TnT levels and third trimester cardiac structure. There was no relationship between fetal TnT or proBNP levels and second trimester cardiac structure.

Cardiac function. There was no significant correlation with cord blood proBNP or TnT and fetal cardiac function in the first, second, or third trimesters (Table 2).

Doppler indexes

When all diabetic patients were included there was a nonsignificant trend toward a positive correlation between TnT and umbilical artery pulsatility index (UAPI) with increased levels of TnT found when UAPI increased ($P = 0.065$). The median A1C in the diabetic cohort in the third trimester was 6.3%. Among patients with third trimester A1C $>6.3\%$, a significant correlation was noted between TnT and UAPI (r coefficient 0.436, $P < 0.05$) (Fig. 1B). There was no association between TnT and middle cerebral artery pulsatility index or ductus venosus pulsatility index. There was no correlation between proBNP and umbilical artery, middle cerebral artery, or ductus venosus Doppler indexes.

Perinatal outcome

Only one infant had clinically recognized cardiomyopathy with fetal proBNP mea-

suring 7,092 pmol/l and TnT measuring 0.07 ng/ml. This diabetic mother presented for assessment at 38 weeks complaining of a 24 history of decreased fetal movements. An emergency cesarean section was performed because of a pathological cardiotocograph, and her infant had an Apgar score of 1 at 1 min and 7 at 5 min with an arterial pH of 7.07. The infant was transferred to the NICU and made a good recovery with expectant management. The initial neonatal echocardiogram showed significant cardiomyopathy, which had resolved completely by the follow-up echocardiogram at day 56 of postnatal age.

Among diabetic pregnancies, there was no significant difference between proBNP or TnT levels in those infants who were admitted to the NICU versus those who were not. However, within the diabetic group fetal TnT was significantly elevated in those infants with poor perinatal outcome (17 poor vs. 27 good, median 0.04 [interquartile range 0–0.11] vs. 0.02 [0–0.02] ng/ml, $P < 0.05$). There was no difference in fetal proBNP levels (poor outcome $n = 14$, 181 [0–378] pmol/l vs. good outcome $n = 28$, 123 [49–197] pmol/l; NS). Whereas no relationship was found in the total group between mode of delivery and TnT or proBNP, within the diabetic cohort increased levels of TnT were noted in infants delivered by emergency intrapartum cesarean section or instrumental delivery for fetal distress/failure to advance com-

pared with those delivered by planned cesarean or spontaneous vaginal delivery (0.03 ± 0.11 vs. 0.00 ± 0.02 ; $P < 0.05$). There was no difference in proBNP levels between these groups. Overall there was no correlation between arterial cord pH and fetal TnT or proBNP in the total group. In particular, among fetuses of diabetic pregnancy alone, the mean ± SD cord TnT value with cord pH ≤ 7.2 was 0.03 ± 0.03 vs. 0.03 ± 0.03 and with cord pH >7.2 was 0.027 ± 0.03 (NS).

CONCLUSIONS— Fetal proBNP and TnT concentrations are higher in fetuses of diabetic mothers than in the normal population. Third trimester interventricular septal thickening correlates with levels of fetal proBNP. In pregnant women with poorly controlled diabetes, abnormal third trimester umbilical artery Doppler index is associated with increased cord blood TnT. In addition, fetuses of diabetic mothers with poor perinatal outcome have higher levels of cord blood TnT.

Neither proBNP nor TnT concentrations in total were significantly associated with mode of delivery, gestational age at delivery, or birth weight, consistent with previous studies (10,18). No relationship was noted between proBNP and Troponin-T and third trimester cardiac function parameters in the diabetic cohort. We have previously described normal cardiac function in this group (9), but the findings in this article suggest that biochemical markers are more sensitive than ultrasonographic measurements in the detection of cardiac dysfunction.

The strengths of this article are that it provides new data on the relationship between fetal TnT and proBNP with cardiac function and structure, glycemic control, fetal and placental Doppler data, and perinatal outcome. Ideally all of the normal cohort would have had an oral glucose challenge test to exclude gestational diabetes. However, none of our patients had a predelivery random glucose value >7 mmol/l, a personal or family history of diabetes, or other risk factors for gestational diabetes. Another potential limitation is the timing of the third trimester assessment of cardiac function. It was performed at 36 weeks, whereas the mean age at delivery was 38 weeks. A fetal echocardiogram closer to delivery may have shown better correlation between biochemical and echocardiographic markers of cardiac function.

Increased proBNP levels in diabetic pregnancies have been reported previously (18,19), but we are the first to demonstrate a relationship with interventricular septal thickening. We have also explored this relationship further by correlation with fetal circulation and detailed echocardiography data. In response to a mild degree of cardiac failure, it is possible that in the fetus proBNP is released to prevent significant cardiac hypertrophy. Similar to our group (21), Halse et al. (18) found increased proBNP in diabetic pregnancies, which was significantly higher in patients with poor glycemic control. Local release of BNP acts as a vasodilator at a placental level (22), thus lowering fetal afterload and preventing cardiomyopathy. Animal work provides further evidence that natriuretic peptides have a role in cardiomyopathy prevention. Both atrial natriuretic peptide and BNP bind to the same receptor, the natriuretic peptide receptor (NPR-A). An animal model using the NPR-A knockout mouse (*Npr^{-/-}*) shows that these mice have elevated blood pressure and marked cardiac hypertrophy and fibrosis at birth (18). The role of NPR-A in inhibiting cardiac hypertrophy seems to be even more important in the presence of hypoxia (23). Gopinath et al. (24) found that mRNA levels for the atrial natriuretic peptide gene were significantly higher in left ventricular tissue from neonates of diabetic mothers than from those control mothers, followed by an 18-fold decrease in mRNA from the 1st to the 28th neonatal day in comparison with a fivefold decrease in the control neonates during the same time with no difference between the cohorts by day 28. This model fits with the regression in diabetic cardiomyopathy that is usually seen in the postnatal period. In our earlier work (9), we demonstrated changes in cardiac function in the first trimester in the diabetic population, which preceded functional changes seen in the third trimester. Cardiac hypertrophy in the fetus, namely a thickened intraventricular wall, could imply elevated afterload, which may explain the high levels of proBNP circulating as an antihypertrophic factor. ProBNP release may decrease but not prevent the development of significant fetal cardiomyopathy.

We are the first group to look at TnT in fetuses of type 1 diabetic pregnancies, and we found increased levels in this group. We also noted a relationship between increased TnT levels and increased UAPI in pregnant women with poorly

controlled type 1 diabetes. The umbilical artery is a branch of the fetal aorta and is a surrogate marker of blood pressure in the fetal arterial circulation and thus a measure of fetal afterload. Diabetic vasculopathy is known to affect decidual vascular histology, causing fibrinoid necrosis, atherosclerosis, and thrombosis, and significantly higher resistance indexes are found in the uterine arcuate arteries classified as vasculopathic (25). Troponin release occurs in response to ischemia, and it is possible that increased downstream resistance due to placental vasculopathy causes a degree of hypoxia that affects the fetal myocardium. Pietryga et al. (26) found a correlation between A1C and increased fetal umbilical artery resistance in those with known pregestational vasculopathy, which could reflect diabetes-induced placental microvascular disease. Abnormal placentation may lead to chronic intrauterine hypoxia, which could affect fetal myocardial function, making diabetic fetuses more susceptible to an acute hypoxic insult (27,28).

These data suggest that maternal pregestational type 1 diabetes is associated with significant effects on fetal cardiac function with correlation between interventricular septal thickening and proBNP release in diabetic pregnancy. Poor glycemic control in early pregnancy may change fetal cardiac gene activation and predispose the fetus to myocardial hypertrophy, which explains why hypertrophy can develop even in the presence of good glycemic control later in pregnancy. The BNP/NPR receptor pathway may thus be involved in the third trimester cardiomyopathy so commonly seen in diabetic pregnancy. Early pregnancy hyperglycemia may also have an effect on the developing placenta and impaired placental functioning may result in chronic intrauterine hypoxia causing ischemic damage to the fetal myocardium and thus TnT release.

This article adds to the body of literature on diabetic cardiomyopathy and our understanding of the pathways involved. Because poor control in early pregnancy is a recognized risk factor for late intrauterine death, it is possible that hyperglycemia-induced fetal programming may lead to a susceptibility to cardiomyopathy and “unexplained” intrauterine death. Further genomic and proteomic studies of the effect of hyperglycemia and hyperinsulinemia on the diabetic placenta and the developing myocardium may provide more answers.

This article further emphasizes the need for stringent glycemic control, both preconceptually and in early pregnancy.

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