Fetal cardiovascular hemodynamics in type 1 diabetic pregnancies at near term gestation.

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Abstract

Objectives: Poor glycemic control in maternal type 1 diabetes (T1DM) during pregnancy can affect fetal cardiac and placental function. However, studies concerning fetal central hemodynamics have revealed conflicting results. We hypothesized that in pregnancies complicated by maternal T1DM with adequate glycemic control, fetal cardiovascular and placental hemodynamics are comparable to the control fetuses at near term gestation. In addition, we investigated the relationship between newborn serum biomarkers of cardiac function and fetal cardiovascular and placental hemodynamics. Furthermore, we studied, whether maternal diabetes is associated with placental inflammation.

Methods: In this prospective case-control study, fetal central and peripheral hemodynamics were assessed by ultrasonography in 33 women with T1DM and in 67 controls with singleton pregnancies between 34+2 and 40+2 gestational weeks. Newborn umbilical cord serum was collected to analyze cardiac natriuretic peptides (atrial and B-type natriuretic peptides) and troponin T concentrations. Placental tissue samples were obtained for cytokine analyses.

Results: Fetal ventricular wall thicknesses were greater and weight-adjusted stroke volumes and cardiac outputs were lower in the T1DM group than in the control group. Pulsatility in the aortic isthmus and inferior vena cava blood flow velocity waveforms was greater in the T1DM group fetuses than in the controls. A positive correlation was found between branch pulmonary artery and aortic isthmus pulsatility index values. Umbilical artery pulsatility indices were comparable between the groups. Umbilical cord serum natriuretic peptide and troponin T concentrations were elevated in the T1DM fetuses. These cardiac biomarkers correlated significantly with cardiovascular hemodynamics. Placental cytokine levels were not different between the groups.

Conclusions: In maternal T1DM pregnancies, fetal cardiovascular hemodynamics is impaired, even with adequate glycemic control. Maternal T1DM does not seem to alter placental vascular impedance or induce placental inflammation.

Keywords: aortic isthmus, branch pulmonary artery, cardiac dysfunction, Doppler ultrasound, natriuretic peptide, placenta, type 1 diabetes

Abbreviations:

ANP, atrial natriuretic peptide

AoI, aortic isthmus

BMI, body mass index

BNP, B-type natriuretic peptide

BPA, branch pulmonary artery

CCO, combined cardiac output

CO, cardiac output

DV, ductus venosus

E/A-ratio, ratio of velocity-time integrals of early ventricular and atrial contractions

gHbA1c, glycated hemoglobin

ICT, isovolumetric contraction time

IGF, insulin-like growth factor

IL, interleukin

IMP, index of myocardial performance

IRT, isovolumetric relaxation time

IVC, inferior vena cava

LV, left ventricle

MCA, middle cerebral artery

NT-proANP, N-terminal fragments of ANP

NT-proBNP, N-terminal fragments of BNP

PI, pulsatility index

PIV, pulsatility index for veins

RV, right ventricle

T1DM, type 1 diabetes mellitus

TnT, cardiac troponin T

UA, umbilical artery

Key message: In pregnancies complicated by maternal type 1 diabetes, fetal cardiovascular hemodynamics is impaired, even with adequate glycemic control. Maternal type 1 diabetes does not seem to affect placental vascular impedance or induce placental inflammation.

Introduction

Maternal hyperglycemia results in fetal hyperglycemia causing excess fetal pancreatic β-cell growth. [1] Hyperinsulinemia has anabolic and mitogenic effects, and increases circulating growth factor levels. [2] Fetal sheep studies have shown that increased arterial blood pressure combined with elevated circulating insulin-like growth factor (IGF), natriuretic peptide, and angiotensin II concentrations increase fetal cardiac growth. [3] Newborns of mothers with type 1 diabetes (T1DM) have elevated cord serum levels of natriuretic peptides, [4] cardiac troponin T (TnT), [5] angiotensin II, [6] and growth factors. [2] Increased umbilical cord serum concentrations of atrial (ANP) and B-type natriuretic peptides (BNP) and TnT correlate with increased levels of maternal gHbA1c [4] suggesting that poor maternal glucose control can affect fetal heart.

In pregnancies complicated by maternal T1DM, the incidence of stillbirth is 4-fold and neonatal mortality 2-fold when compared to pregnancies of healthy women. [7] Fetal demise is thought to result from intrauterine hypoxia. Fetal hyperglycemia and hyperinsulinemia increase basal metabolic activity and oxygen consumption. [8] In maternal T1DM pregnancies, placental histology reveals reduced villous membrane diffusion capacity, further enhancing susceptibility to hypoxemia. [9] Furthermore, villous immaturity and other placental abnormalities correlate to umbilical cord IGF-1 levels. [10] Additionally, inflammatory mediators are found in placentas of experimental models of maternal hyperglycemia [11] that may further exacerbate placental oxygen delivery to the fetus.

Surveillance of fetal hemodynamics with Doppler ultrasound reduces perinatal morbidity in high-risk pregnancies, such as maternal T1DM. [12] Studies on fetal cardiac function in maternal T1DM pregnancies have revealed conflicting results. [13,14] Increased myocardial wall thicknesses have been reported and the wall thickness seems to correlate with circulating cord blood IGF-1 levels. [15] Good maternal glucose control in early pregnancy is critical, since biochemical markers of fetal cardiac dysfunction at birth are increased in pregnancies with poor glycemic control in the first trimester. [16] In late term fetuses of maternal T1DM, the pulsatility of umbilical artery (UA) blood flow velocity waveform that reflects the capacity of placental tertiary villous arterioles, is decreased in macrosomic fetuses. [17] However, if maternal glycemic control is poor or

diabetes is associated with vasculopathies, pulsatility of UA blood flow velocity waveform can be increased. [4]

We hypothesized that, in adequately controlled T1DM pregnancies, fetal cardiovascular and placental hemodynamics are comparable to the control group fetuses at near term gestation. In addition, we investigated newborn umbilical cord serum biochemical markers of cardiac function and their correlation with cardiovascular hemodynamic parameters. Finally, we explored whether maternal T1DM is associated with placental inflammation.

Material and Methods

Study population

This prospective case-control study was carried out at Turku and Oulu University Hospitals, Finland. For this study, a total of 33 T1DM and 67 healthy women (control group) were included. The women with T1DM were recruited consecutively at the University Hospital outpatient maternity clinics during their first visit to avoid any selection bias. For the control group, women were recruited at the outpatient maternity clinics. Inclusion criteria were age < 35 years, singleton pregnancy and a normal fetal anatomic survey at around 20 weeks of gestation, and for the control group women BMI < 30, no major serious illnesses and a normal 2-hour oral glucose tolerance test at 24-28 gestational weeks. Obese women were excluded from the control group since hyperglycemia and insulin resistance often complicate these pregnancies. All women signed an informed consent form. Gestational age was confirmed by ultrasonography at the end of the first trimester. Maternal and neonatal outcome parameters were obtained from the hospital records.

Ultrasonography

Transabdominal ultrasound imaging (Acuson Sequoia 512, Mountain View, CA, USA) was performed with an 8-MHz convex transducer (M.H., L.L.). The ultrasonographic data collected closest to the delivery, between 34+2 and 40+2 gestational weeks, was used for this study. The high pass filter was set at a minimum. An angle of ≤20 degrees between the vessel and the Doppler beam was considered

acceptable. The mean value from three consecutive cardiac cycles was used for further analysis. Mechanical and thermal indices were kept <1.0. Pulsed- and color-Doppler examinations were videotaped and analyzed offline.

Image-directed pulsed and color-Doppler was used to record mitral and tricuspid valve blood flow velocity waveforms from the four-chamber view of the heart. Velocity-time integral -ratio between early ventricular and atrial contraction filling (E/A-ratio) was calculated to estimate cardiac diastolic function. The outflow blood flow velocity waveforms were recorded at the level of pulmonary and aortic valves. The valve diameters were measured using the leading-edge-to-leading-edge method in systole. The cross-sectional area of the valve was calculated. Velocity-time integral was obtained by planimetering the area of the Doppler spectrum. Volume blood flows across the aortic and pulmonary valves were calculated (cross-sectional area x velocity-time-integral -ratio x fetal heart rate). Left (LV) and right (RV) ventricular stroke volumes (SV), and cardiac outputs (CO) were indexed for fetal weight. The sum of LVCO and RVCO equals combined cardiac output (CCO). Fetal heart rate adjusted LV isovolumetric relaxation time (IRT%), contraction time (ICT%), and index of myocardial performance (IMP = ICT + IRT / ejection time) were calculated to assess fetal LV diastolic, systolic, and global function. [18]

M-mode recordings were obtained from a four-chamber view to measure the ventricular wall and interventricular septal thicknesses at the atrioventricular valve level. End-diastolic measurements were taken at maximal chamber dilatation.

The blood flow velocity waveforms of the UA, descending aorta, ductus arteriosus, aortic isthmus (AoI), middle cerebral artery (MCA), proximal right or left branch pulmonary artery (BPA), inferior vena cava (IVC), ductus venosus (DV) and pulmonary vein were obtained, and pulsatility index [PI=(peak systolic velocity—end-diastolic velocity)/ time-averaged maximum velocity over the cardiac cycle] and PI for veins (PIV) [PIV=(peak systolic velocity—velocity during atrial contraction)/time-averaged maximum velocity over the cardiac cycle] values were calculated. Fetal heart rate was measured from the UA blood flow velocity waveform.

Intra- and interobserver variabilities were calculated for LV stroke volume by analyzing the blood flow velocity waveforms from measurements on the same patient

by two researchers (MH and LL) and twice by the same researcher (LL). In addition, interobserver variability for DV blood flow velocity waveform was calculated.

Newborn blood samples

Immediately after delivery, umbilical cord blood samples were collected. Newborn umbilical artery acid base status was determined. Cardiac ANP and BNP are initially synthesized as inactive prohormones, and cleaved in equimolar amounts to ANP and BNP and inactive N-terminal fragments (NT-proANP, NT–proBNP) respectively. Umbilical cord serum concentrations of NT-proANP and NT-proBNP were measured by radioimmunoassays. [19] The sequences recognized by NT-proANP and NT-proBNP antisera were $proANP_{46-79}$ and $proBNP_{10-29}$. Detection limit for NT-proANP and NT-proBNP were 60 pmol/l and 40 pmol/l. Troponin T (TnT) concentration was measured by electrochemiluminescence immunoassay (TYKSLAB, Turku, Finland). The detection limit was set at <0.014 ng/ml.

Placental samples

Placental tissue samples were collected within 2 hours after delivery and samples from diabetic pregnancies were paired with a sample of a control placenta of similar gestational age (±4 days). Samples were stored at -80°C until analysis.

Cytokine levels were measured from 24 T1DM and 25 control placental samples. The concentrations of interleukins IL1β, IL6, IL10, and tumor necrosis factor alfa (TNFα) (Bio-Plex Pro Human Cytokine 8-Plex Immunoassay, Bio-Rad, Hercules, CA) were considered as markers of placental inflammation. The assay was performed according to the manufacturer's instructions using Bio-Plex MAGPIX Multiplex Reader in duplicate.

Statistical analyses

The data was tested for normality. When required by the statistical distribution, a logarithmic scale or √x conversion was utilized. Two-way comparisons were performed by Student's T-test. The categorical variables were tested for significance using Mantel-Haenszel chi-square or Fisher's exact test (for variables with less than 5 entries) method. All correlations were tested with Pearson's correlation (R[X=n-2,

degrees of freedom]). The statistical analyses were performed using SAS (SAS Institute, Cary, NC). The level of significance was set at $p<0.05$.

Ethical approval

The Ethics Committee in the Hospital Districts approved the research protocol (license 167/2005 §183, dated May 17, 2005).

Results

Women with T1DM had more often hypertension, thyroid dysfunction, and preeclampsia. In the T1DM group, the mean gHbA1c concentrations decreased from prepregnancy values with advancing gestational age (Table 1).

The ultrasound examination was performed at 250 (±13) gestational days in T1DM group and at 262 (±13) days in the controls. The mean time interval from the ultrasound examination to delivery was comparable between the groups, 12 (±10) and 14 (±8) days for the T1DM and control groups. Mothers with T1DM had more often labor induction or cesarean section prior to 37 gestational weeks. There was no difference in the umbilical artery pH values between the groups. The incidence of LGA newborns (birth weight ≥ +2 SD) was higher, and the need of phototherapy due to neonatal jaundice and neonatal intensive care unit admissions were more common in the neonates of T1DM mothers (Table 2).

Fetal heart rate was higher in T1DM fetuses. Ventricular and interventricular septal end-diastolic wall thicknesses were increased in the T1DM group when compared to controls. Both weight-adjusted RV and LV SV and CO, as well as combined CO were lower in the T1DM group fetuses than in the control group. The LV IRT%, ICT% and IMP did not differ between the groups. However, MV E/A-ratio was lower in the T1DM group fetuses compared to the controls. Pulsatility indices in the AoI and IVC were greater in the T1DM than in the control fetuses (Figure 1, Table 3). Pulsatility indices in other arteries and veins did not differ between the groups. AoI PI values correlated positively ($R(85)=0.532$, 95% CI 0.368-0.754, $p<0.001$) with BPA PI values. TV E/A-ratio correlated negatively with RV wall ($R(58)=-0.293$, 95% CI -0.479-(-

0.037), p=0.023) and interventricular septal (R(58)=-0.257, 95% CI -0.449-(-0.002), p=0.048) thicknesses.

The newborn umbilical cord serum concentrations of NT-proANP, NT-proBNP, and TnT were significantly higher in the T1DM than in the control group. Placental interleukin and TNFα levels were comparable between the groups (Table 4). Umbilical artery PI values correlated positively with NT-proBNP and LVCO correlated negatively with umbilical cord serum TnT concentration. Aortic isthmus PI values showed positive correlations with NT-proANP, NT-proBNP and TnT concentrations in the umbilical cord serum (Table 5). Mode of delivery did not affect any of the measured newborn serum biomarker concentrations or placental cytokine levels.

Inter- and intraobserver variabilities for LV stroke volume were 2.4 % and 3.5 % (95% CI, 0.9–5.2%). Interobserver variability for DV PIV was 5.3% (95% CI, 1.5–10.1%).

Discussion

Maternal T1DM affects the fetal heart by increasing its wall thicknesses. In addition, weight-adjusted stroke volumes and cardiac outputs were decreased in the T1DM group at near term gestation. A significant positive correlation between the aortic isthmus and BPA PI values suggests that fetal pulmonary circulation has an important role in the maintenance of LVCO and aortic isthmus hemodynamics. On the other hand, placental vascular impedance was not compromised and there was no evidence of placental inflammation in maternal T1DM pregnancies.

In maternal T1DM, we found increased fetal myocardial wall thicknesses as demonstrated previously. [4,14] In experimental studies, high maternal glucose concentrations directly increase fetal cardiac septal growth. [20] However, increased fetal interventricular septal thickness is found also in T1DM mothers with good glycemic control. [21] We observed that fetal weight-adjusted cardiac SV and CO measurements from both ventricles, and mitral valve E/A-ratio were decreased. Furthermore, we found negative correlations between cardiac wall thicknesses and tricuspid valve E/A-ratio. Our findings suggest that the excess cardiac wall thickness may affect the active relaxation process of the myocardium. Thus, it seems that at near term gestation, fetal

left ventricular filling is more dependent on atrial contraction in maternal T1DM pregnancies. However, the other indices of left ventricular function were comparable to the control group suggesting that functional disturbances could be rather subtle.

We found increased pulsatility of IVC blood flow velocity waveform in T1DM group fetuses, while DV PIV values were comparable between the groups. An increase in the pulsatility of systemic venous or DV blood flow profile could indicate elevated ventricular end-diastolic pressure and a rise in systemic venous pressure. Another cause is augmented atrial contraction that would be the most likely explanation in our study. Our findings suggest that IVC blood flow profile could be more sensitive than DV to changes in cardiac function, at least in maternal T1DM pregnancies. It must be kept in mind that DV blood flow profile is also affected by the amount of umbilical venous blood return from the placenta and the caliber of DV that is mainly regulated by fetal pO_2.

The pulsatility of fetal AoI blood flow velocity waveform was greater in T1DM pregnancies than in the controls at near term gestation. In fetal circulation, AoI has an important physiologic role allowing communication between the LV and RV outputs that are arranged in parallel. Aortic isthmus represents the arterial watershed between the upper (including brain) and lower (including placenta) body circulations. [22] Normally, there is antegrade blood flow across the AoI towards the descending aorta throughout gestation. [23] In diastole, when the semilunar valves are closed, direction of blood flow across the AoI is mainly affected by cerebral and placental vascular resistances. [24] Adequate central hemodynamics, in specific LVCO, are important in maintaining antegrade flow across the aortic isthmus. In the present study, UA and MCA PI values did not differ between the groups suggesting that the placental and cerebral vascular impedances were comparable between the groups. Importantly, we found a positive correlation between AoI and BPA PI values. In other words, pulmonary vasoconstriction was associated with increased pulsatility in the AoI blood flow velocity waveform. During pulmonary vasoconstriction fetal lung volume blood flow decreases thus reducing blood flow return to the left atrium and ventricle. Fetal sheep studies suggest that foramen ovale cannot substantially increase its volume blood flow. [25] Our findings suggest that fetal lung circulation has an important role in the maintenance of LVCO and normal hemodynamics in the AoI.

In this study, umbilical cord serum natriuretic peptide and TnT concentrations were elevated in the maternal T1DM group thus confirming the observations of previous studies. [4,16] We propose that increased circulating natriuretic peptide levels reflect increased myocardial mass rather than are markers of cardiac dysfunction, because natriuretic peptides regulate and prevent excess cardiomyocyte growth. [26] Furthermore, BNP, and to a lesser extent ANP, are vasodilators that reduce cardiac afterload in the fetus. [27] This is supported by the finding that NT-proBNP levels correlated with placental vascular impedance. Our results suggest that fetal weight-adjusted systemic vascular resistance is increased in T1DM pregnancies, because fetal CCO was significantly lower than in the control group. In addition, TnT that is considered as a cardio-specific marker of myocardial cell damage[5] had a negative correlation with LVCO further strengthening the concept that increased myocardial cell mass has a negative impact on ventricular function, i.e. producing adequate cardiac output. Finally, AoI pulsatility index values correlated with cardiac natriuretic peptide and TnT secretions demonstrating that AoI blood flow pattern can reflect alterations in fetal cardiac performance.

In T1DM pregnancies, UA vascular impedance was not different from the control group suggesting that functional capacity of placental tertiary villous arterioles was adequate and comparable to the control pregnancies. Furthermore, no evidence of placental inflammation was noted in T1DM pregnancies. One limitation of our study is that we did not perform any placental histologic examination. Previously, histological abnormalities in the placenta have been observed in T1DM pregnancies. In an experimental rat model of untreated maternal pregestational hyperglycemia, fetal cardiac hyperplasia and dysfunction, abnormal expression of cardiac and placental genes, and signs of placental insufficiency were seen at near term gestation. [11,28] This could indicate that adequate glycemic control during pregnancy could prevent placental abnormalities, at least to certain degree.

Intra- and interobserver variabilities tested in this study were comparable to previous studies on volumetric blood flows. [29] Fetal ultrasound was performed at earlier gestational age in the T1DM group than in the controls and this could be a confounding factor. However, it is well known that fetal hemodynamic parameters remain constant throughout the third trimester, [30] and we adjusted fetal cardiac output measurements for

estimated fetal weight. One of the strengths of this study is that we used several methods and approaches to assess fetal well-being and placental function. Another strength is that we recruited our diabetic patients consecutively thus minimizing any selection bias.

Conclusion

This study was designed to investigate fetal cardiovascular and placental function and hemodynamics in maternal T1DM pregnancies at near term gestation. The most important finding was that even when maternal glycemic control is adequate, fetal cardiovascular hemodynamics is impaired, including decreased cardiac output and increased pulsatility in the aortic isthmus blood flow velocity waveform. On the other hand, placental hemodynamics is maintained with no evidence of placental inflammation.

Tweetable Abstract (22 words): In pregnancies complicated by maternal type 1 diabetes, fetal cardiac output is reduced, even in the presence of adequate glycemic control.

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Table 1. Maternal characteristics.

Variable	Control	T1DM	*p*
n	**67**	**33**	
Maternal prepregnancy characteristics			
Maternal age (years)	28.0 ± 4.0	28.5 ± 4.9	0.620
Prepregnancy BMI (kg/m2)	23.2 ± 3.4	26.1 ± 4.9	NA
Smoking	2 (3.0)	5 (15.2)	<0.0001
Nulliparous	42 (62.7)	17 (51.5)	0.173
White class			
B		6 (18.2)	NA
C		8 (24.2)	NA
D		6 (18.2)	NA
R		8 (24.2)	NA
F, D+R, R+F		6 (18.2)	NA
gHbA1c%		7.9 ± 1.6	NA
Hypertension	3 (4.5)	5 (15.2)	0.027
Pregnancy characteristics			
gHbA1c% (32 weeks)		6.4 ± 0.9	NA
Incidence of hypoglycemia (<2,6 mmol/l)		15 (45.5)	NA
Basal insulin dose (30 weeks)		49.0 ± 20.5	NA
Prandial insulin dose (30 weeks)		42.6 ± 19.5	NA
Retinopathy during pregnancy		20 (60.6)	NA
Nephro- or neuropathy		6 (18.2)	NA
Hypertension or pre-eclampsia	6 (9.0)	11 (23.3)	0.010

T1DM, type 1 diabetes mellitus; gHbA1c%, glycated hemoglobin content.

Data are means ± SD, or no of cases (%).

Table 2. Pregnancy outcome.

Variable	Control	T1DM	*p*
n	67	33	
Delivery			
Prematurity (<37 weeks)	6 (9.0)	11 (33.3)	0.002
GA at delivery (weeks)	39.5 ± 1.9	37.4 ± 1.5	<0.0001
Induction of labor (%)	15 (22.4)	14 (42.4)	0.038
Mode of delivery			<0.0001
Vaginal (%)	50 (74.6)	13 (39.4)	<0.0001
Vaginal operative (%)	7 (10.4)	2 (6.1)	NA
Cesarean section (%)	10 (14.9)	18 (54.5)	<0.0001
Elective (%)	3 (4.5)	13 (39.4)	NA
Other (%)	7 (10.4)	5 (15.2)	NA
Neonatal characteristics			
Umbilical artery pH	7.3 ± 0.1	7.3 ± 0.1	0.791
Birth weight (g)	3505 ± 556	3686 ± 599	0.144
IUGR (%)	3 (4.5)	-	NA
LGA (%)	2 (3.0)	11 (33.3)	NA
Phototherapy (%)	9 (13.4)	9 (27.3)	0.023
NICU admission (%)	7 (10.4)	24 (72.7)	<0.0001

T1DM, type 1 diabetes mellitus; GA, gestational age; IUGR, intrauterine growth restriction; LGA, large for gestational age; NICU, neonatal intensive care unit. Data are means ± SD, or no of cases (%).

Table 3. Hemodynamic data of the study groups

Variable	Control	T1DM	*p*
n	67	33	
Gestational week	37+3 ± 1+6	35+5 ± 1+6	<0.0001
Central hemodynamics			
FHR (bpm)	137.4 ± 10.7	144.3 ± 13.4	0.007
TV E/A-ratio	0.66 ± 0.22	0.63 ± 0.30	0.537
MV E/A-ratio	0.83 ± 0.29	0.66 ± 0.27	0.006
RV stroke volume (ml)	3.19 ± 1.16	2.47 ± 1.32	0.009
RVCO (ml/min*kg)	369.1 ± 85.5	220.1 ± 93.4	<0.0001
LV stroke volume (ml)	2.09 ± 0.78	1.71 ± 0.85	0.024
LVCO (ml/min*kg)	247.9 ± 61.5	162.3 ± 65.9	<0.0001
CCO (ml/min*kg)	619.2 ± 129.5	405.9 ± 184.5	0.001
IMP (LV)	0.43 ± 0.10	0.43 ± 0.09	0.775
IRT%	10.5 ± 2.8	10.4 ± 2.0	0.856
ICT%	6.7 ± 2.3	6.3 ± 1.9	0.376
RVW diastole (mm)	3.5 ± 0.6	5.6 ± 2.6	<0.0001
IVS diastole (mm)	3.5 ± 0.9	5.8 ± 3.0	<0.0001
LVW diastole (mm)	3.5 ± 0.7	4.5 ± 0.8	<0.0001
Peripheral hemodynamics			
UA PI	0.88 ± 0.20	0.73 ± 0.41	0.135
MCA PI	1.58 ± 0.47	1.67 ± 0.71	0.372
AoI PI	3.77 ± 0.76	7.23 ± 4.42	0.025
DAo PI	1.97 ± 0.44	1.92 ± 0.41	0.316
BPA PI	4.51 ± 1.73	6.08 ± 2.64	0.281
IVC PIV	1.70 ± 0.43	2.01 ± 0.34	0.001
DV PIV	0.50 ± 0.18	0.53 ± 0.10	0.746

T1DM, type 1 diabetes mellitus; FHR, fetal heart rate; TV E/A-ratio, tricuspid valve E- to A-wave ratio; MV E/A-ratio, mitral valve E- to A-wave ratio; RV, right ventricle; RVCO, RV cardiac output; LV, left ventricle; LVCO, LV cardiac output; CCO,

combined cardiac output, IMP, index of myocardial performance; IRT%, isovolumetric relaxation time adjusted for fetal heart rate; ICT%, isovolumetric contraction time adjusted for fetal heart rate; RVW, right ventricular wall thickness; IVS, interventricular septum thickness; LVW, left ventricular wall thickness; UA, umbilical artery; PI, pulsatility index; MCA, middle cerebral artery; AoI, aortic isthmus; DAo, ductus arteriosus; BPA, branching pulmonary artery; IVC, inferior vena cava; DV, ductus venosus.

Data are means ± SD.

Table 4. Umbilical cord blood and placental sample data.

Variable	Control	T1DM	*p*
Umbilical cord blood			
n	**67**	**33**	
NT-proANP (pmol/l)	2134.0 ± 945.6	2956.7 ± 1304.4	0.003
NT-proBNP (pmol/l)	383.8 ± 267.7	710.4 ± 488.4	<0.0001
TnT (ng/ml)	0.014 ± 0.008	0.033 ± 0.032	<0.0001
Placenta			
n	**25**	**24**	
IL1β (pg/mg prot)	< 6.58	< 6.58	NA
IL6 (pg/mg prot)	20.63 ± 29.44	31.89 ± 77.61	0.558
IL10 (pg/mg prot)	< 7.08	< 7.08	NA
TNFα (pg/mg prot)	6.13 ± 0.46	6.18 ± 0.78	0.767

T1DM, type 1 diabetes mellitus; NT-proANP, N-terminal fragments of atrial natriuretic peptide; NT-proBNP, N-terminal fragments of B-type natriuretic peptide; TnT, cardiac troponin T; IL, interleukin; TNFα, tumor necrosis factor α.

Data are means ± SD.

Figure legends.

Figure 1.

Aortic isthmus blood flow velocity waveforms.

In upper panel, a waveform from a control group fetus that shows a normal small early-diastolic retrograde component and antegrade diastolic flow (arrow). In lower panel, a waveform from a T1DM group fetus demonstrating increased pulsatility in the blood flow profile. Early-diastolic retrograde component is larger and diastolic flow is retrograde.