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LETTER TO THE EDITOR

Cardiovascular Health of Offspring of Diabetic Mothers From the Fetal Through Late-Infancy Stages

Clinical and experimental data suggest that maternal diabetes mellitus (MDM) has transgenerational consequences with a high incidence of cardiovascular disease (CVD) observed in adult offspring. Infants of DM mothers (IDMs) are known to evolve ventricular hypertrophy and diastolic dysfunction in utero. Although it is assumed these changes resolve postnatally within months, there are insufficient supportive data. Animal models provide evidence that MDM may also affect the vascular health of MDM offspring (1). We performed a longitudinal case-control study to investigate whether fetal myocardial abnormalities in MDM persist in later infancy, IDMs demonstrate increased aortic stiffness, and cardiovascular abnormalities relate to worse maternal glycemic control.

After informed consent, pregnant mothers with insulin-dependent pre-gestational diabetes and healthy controls (no maternal illness, normal glucose testing) underwent serial fetal echocardiography (at 18 to 24, 26 to 30, and 32 to 36 weeks of gestation), and their infants underwent postnatal echocardiography (at 2 to 6 weeks and 6 to 12 months). We excluded pregnancies with major fetal abnormalities, growth restriction (birth weight <10th percentile), or preterm delivery (≤34 weeks). Hemoglobin A1c was recorded for all 3 trimesters in MDM pregnancies. Echocardiographic evaluations included assessment of left ventricular (LV) posterior wall (LVPWd) and interventricular septal (IVSd) thickness in diastole and mass, systolic and diastolic function (prenatal and postnatal), and aortic pulse wave velocity (PWV; postnatal only).

Thirty-six MDM and 36 control pregnancies were studied. MDM A1c at each trimester was 7.2 ± 1.1, 6.8 ± 0.9, and 6.6 ± 0.9, respectively. Maternal age, gravity, parity, body mass index, blood pressures, delivery method, gestational age, biparietal diameter and femur length at fetal echo, gestational age at delivery, infant gender, birth weight and length, and postnatal weight, length, and age at echo did not differ between groups.

IDM fetuses demonstrated increased LVPWd and IVSd thickness compared with controls from late second through third trimesters and increased mitral valve Doppler velocities and LV Tei index in the third trimester (Table 1). Heart rate and other function indices did not differ between groups. In early and late infancy, IDMs demonstrated persistently increased LVPWd and IVSd (z-scores) and indexed LV mass. Greater LVPWd and IVSd in late gestation were associated with greater postnatal LVPWd and IVSd z-scores ($p < 0.001$). Of LV function indices, only LV Tei index was increased in IDMs in late infancy (0.43 ± 0.05 vs. 0.33 ± 0.07; $p = 0.05$). Aortic PWV was significantly increased in IDMs in late infancy (3.7 ± 1.2 m/s vs. 2.3 ± 1.0 m/s; $p < 0.001$) and correlated with third trimester fetal ($R^2 = 0.79$; $p < 0.001$ for both) and late infancy ($R^2 = 0.88$ and 0.85, respectively; $p < 0.001$) LVPWd and IVSd. Late-infancy PWV in IDMs demonstrated a strong positive correlation with third trimester A1c only ($R^2 = 0.84$; $p < 0.001$), whereas LVPWd and IVSd showed no significant correlations with A1c at any gestational age.

Our findings suggest increased LV mass persists in IDMs from mid-gestation through late infancy. IDMs also demonstrate increased aortic stiffness in late infancy. That IDM late infancy aortic PWV correlated with LV wall thickness in late gestation and infancy could support a causal association or common intrauterine insult that could contribute to longer-term CVD risks.

Maternal hyperglycemia has been suspected to be responsible for MDM-related fetal cardiomyopathy; however, this was not supported by our observations. Increased LV mass in late infancy, long after the intrauterine exposure has been removed, suggests other factors likely contribute. Correlations between late-gestation A1c and aortic stiffness in late-infancy IDMs provide further insight into the pathogenesis of the cardiovascular pathology of IDMs. Hyperglycemia in adult diabetes is known to contribute to inflammation and oxidative stress, which leads to structural and functional cardiovascular changes (2,3). Increased inflammatory biomarkers found in cord blood of MDM pregnancies and altered activity of genes responsible for vascular development, integrity, and function (4) may play a role in altered aortic composition that, in turn, could result in altered ventricular afterload and changes in LV mass. Our data suggest the window of fetal vulnerability may be the third trimester, which could imply that both gestational and pre-gestational MDM pregnancies are at risk.

TABLE 1 Comparison of Findings in Fetal and Infant IDMs Versus Controls

	Control	IDM
Birth data		
Birth weight	3.39 ± 0.89	3.4 ± 1.2
Birth length	50.2 ± 7.5	50.2 ± 10.2
Gender (F/M)	20/16	17/19
Fetal assessments		
First examination (weeks)	20.5 ± 2.3	20.5 ± 2.4
IVSd (cm)	0.20 ± 0.02	0.20 ± 0.02
LVPWd (cm)	0.19 ± 0.01	0.196 ± 0.02
MV e (cm/s)	25.6 ± 6.3	28 ± 6.3
MV a (cm/s)	42.0 ± 7.9	41.9 ± 7.6
MV e/a	0.62 ± 0.09	0.68 ± 0.1
LV Tei index	0.48 ± 0.04	0.46 ± 0.08
MCA PI	1.70 ± 0.31	1.60 ± 0.33
UA PI	1.2 ± 0.25	1.2 ± 0.3
Second examination (weeks)	28.9 ± 1.3	28.8 ± 1.3
IVSd (cm)	0.31 ± 0.03	0.35 ± 0.04†
LVPWd (cm)	0.31 ± 0.03	0.34 ± 0.03†
MV e (cm/s)	36.0 ± 6.9	38.0 ± 9.5
MV a (cm/s)	40.0 ± 8.9	50.0 ± 16
MV e/a ratio	0.91 ± 0.15	0.8 ± 0.16
LV Tei index	0.44 ± 0.12	0.5 ± 0.1
MCA PI	1.65 ± 0.4	1.80 ± 0.3
UA PI	0.97 ± 0.15	1.02 ± 0.2
Third examination (weeks)	34.4 ± 1.3	34.8 ± 1.8
IVSd (cm)	0.35 ± 0.02	0.41 ± 0.04‡
LVPWd (cm)	0.34 ± 0.03	0.39 ± 0.03‡
MV e (cm/s)	43.6 ± 8.8	50.5 ± 7.7†
MV a (cm/s)	54.0 ± 8.0	59.3 ± 8.0*
MV e/a ratio	0.81 ± 0.15	0.86 ± 0.11
LV Tei index	0.33 ± 0.04	0.46 ± 0.07†
MCA PI	1.50 ± 0.2	1.40 ± 0.3
UA PI	0.94 ± 0.17	0.97 ± 0.15
Postnatal assessments		
Early infancy (weeks)	4.5 ± 0.8	4.5 ± 1.1
IVS *z*-score	0.95 ± 0.6	1.9 ± 0.9‡
LVPWd *z*-score	0.90 ± 0.6	1.8 ± 0.9†
LV mass indexed to BSA	45.8 ± 5.3	54.1 ± 9.2*
Aortic PWV (m/s)	2.3 ± 1.0	2.2 ± 0.8
Late infancy (weeks)	43 ± 2.5	44 ± 2.7
IVS *z*-score	0.90 ± 0.6	1.8 ± 0.8‡
LVPWd *z*-score	0.80 ± 0.6	1.7 ± 0.8‡
LV mass indexed to BSA	46.2 ± 4.8	56.5 ± 9.3*
Aortic PWV (m/s)	2.3 ± 1.0	3.7 ± 1.2*

Values are mean ± SD. All other functional measures including annular and inflow flow velocities, E/e', isovolumic contraction and relaxation times, ejection fraction, and strain and strain rates (postnatal only) did not differ. Comparisons of continuous variables by unpaired *t* test. *$p < 0.05$. †$p < 0.01$. ‡$p < 0.001$.

BSA = body surface area; F = female; IDMs = infants of mothers with diabetes mellitus; IVSd = interventricular septal; LV = left ventricular; LVPWd = left ventricular posterior wall; M = male; MV = mitral valve; MCA = middle cerebral artery; PI = pulsatility index ([peak systolic velocity − end-diastolic velocity]/mean velocity); PWV = pulse wave velocity; UA = umbilical artery.

Our study was limited by small sample size and paucity of MDM pregnancies with poor glycemic control (suggested by A1c values and normal birth weights), which may have influenced our ability to demonstrate subtle differences and relationships. Lack of normative fetal LV wall thickness data prohibited longitudinal analyses.

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