*Cardiology in the Young*

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# Is the child at risk? Cardiovascular remodelling in children born to diabetic mothers

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## Original Article

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## Abstract

*Objective:* The objective of this study was to assess differences in myocardial systolic and diastolic function and vascular function in children 2–5 years of age born to diabetic as compared to non-diabetic mothers. *Methods:* This study was a retrospective cohort conducted in 2016 at The Aga Khan University Hospital, Karachi, Pakistan. It included children between 2 and 5 years of age born to mothers with and without exposure to diabetes *in utero* (n = 68 in each group) and who were appropriate for gestational age. Myocardial morphology and function using echocardiogram and carotid intima media thickness (cIMT) and pulse wave velocity was performed to evaluate cardiac function as well as macrovascular remodelling in these children. Multiple linear regression was used to compare the groups. *Results:* There was no significant difference in cardiac morphology, myocardial systolic and diastolic function, and macrovascular assessment between the exposed and unexposed groups of AGA children. Subgroup analysis demonstrated a significantly decreased mitral E/A ratio in children whose mothers were on medications as compared to those on dietary control (median [IQR] = 1.7 [1.6–1.9] and 1.56 [1.4–1.7], respectively, p = 0.02), and a higher cIMT in children whose mothers were on medication as compared to controls (0.48 [0.44–0.52] and 0.46 [0.44–0.50], respectively, p = 0.03). *Conclusion: In utero* exposure to uncontrolled maternal diabetes has an effect on the cardiovascular structure and function in children aged 2–5 years. However, future work requires long-term follow-up from fetal to adult life to assess these changes over the life course.

Hyperglycaemia in pregnancy, which includes pre-gestational and gestational diabetes mellitus, has serious maternal and fetal consequences.[1] World Health Organisation has projected that by the year 2030, Pakistan will have the fifth highest prevalence of diabetes with approximately 14 million people affected.[2] Further, global age-specific estimates report that approximately 70% of these cases occur in women <30 years of age.[1] This suggests that the proportion of pregnancies complicated with hyperglycaemia will continue to increase.[3] Frienkel's hypothesis of "fuel-mediated toxicity" states that *in utero* exposure to hyperglycaemia and hyperinsulinemia may lead to anthropometric, endocrine, and neurohormonal modifications in the offspring.[4] These alterations can lead to long-term metabolic and cardiovascular disease.[5] Longitudinal studies have demonstrated that children born to diabetic mothers are at increased risk of obesity, hyperlipidaemia, hyperglycaemia, and metabolic syndrome in adulthood.[6–8] Neonates of diabetic mothers are reported to have alterations in cardiac diastolic function such as increased deceleration time, prolonged Tei index, and impaired global functioning assessed through global longitudinal strain.[9,10] These cohorts have included all children of diabetic mothers (small and large for gestational age), and some of the data may be skewed due to the extreme populations included in this group. As appropriate for gestational-age children most commonly born to diabetic mothers, it is essential to establish their cardiovascular risk.[11] Moreover, the children in these studies do not have objective data on cardiovascular dysfunction and have not been followed to assess the persistence of these changes during childhood. Moreover, the sample size for these studies was small (range 20–40) and hence inadequately powered.[9,10]

The objective of this study was to assess differences in myocardial systolic and diastolic function, global myocardial strain, and vascular function (using carotid intima media thickness [cIMT] and pulse wave velocity [PWV]) in children 2–5 years of age born (appropriate for gestational age) to diabetic as compared to non-diabetic mothers.

## Materials and methods

This study was a retrospective cohort design[12] where maternal hyperglycaemia of the exposed and unexposed groups was retrospectively identified from maternal cohorts, while the



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cardiovascular evaluation was done for children between 2 and 5 years of age at The Aga Khan University Hospital, Karachi, Pakistan. This study was conducted from February to November, 2016. The inclusion criteria for the exposed group were children between 2 and 5 years of age at the time of enrolment with a history of diabetes in the mother during pregnancy as tested by a positive oral glucose tolerance test between 24 and 28 weeks of gestation. The inclusion criteria for the unexposed group were children between 2 and 5 years of age born to mothers with a normal oral glucose tolerance test. The exclusion criteria for both groups were presence of birth weight <2.5 or >4 kg, chromosomal abnormalities, congenital heart disease, and history of pre-eclampsia or any other known medical comorbidities in the mother.

For sample size calculation, previous studies have used differences in the ratio of pulse wave Doppler (PWD)-derived early diastolic filling velocity of the left ventricle (E) to tissue Doppler imaging (TDI)-derived early diastolic myocardial velocity (E′) as it has a high sensitivity to detect subclinical changes in cardiac functional parameters in children.[13,14] Based on these, a sample size of 65 children in each group for E/E′ was calculated (using World Health Organisation sample size calculator version 2.0) to enable us to observe a 20% difference between the exposed and unexposed groups, with 90% power and 5% level of significance. This sample size would also be adequate to detect a difference in cIMT[15] based on the given assumptions.

This study was approved by the Ethics Review Committee at The Aga Khan University. Written informed consent was obtained from either parent. Weight (kg) and height (cm) of the child was recorded using a weighing scale with a stadiometer (Detecto Scales Inc. WS#149). Resting blood pressure of the child (in supine position) in right and left upper extremities was manually recorded using an aneroid cuff by a trained cardiovascular technician. The readings were then averaged for systolic and diastolic values. All echocardiographic examinations were performed using the GE Healthcare Vivid E9 machine (GE Healthcare, Waukesha, WI, USA). Cardiac morphological parameters included sphericity index (base to apex length/basal diameter of the ventricle) (Fig 1) for both ventricles (in a four-chamber view) and left ventricle (LV) relative wall thickness (in parasternal long-axis view).

LV systolic functional measurements included ejection fraction (EF), stroke volume, cardiac output, and mitral annular systolic plane excursion (MAPSE), while tricuspid annular systolic plane excursion (TAPSE) and systolic annular peak velocity (S′) were measured to assess the RV systolic function. Mitral inflow peak early filling (E) velocity, peak atrial filling (A), wave velocity, E/A ratio, deceleration time, and E/E′ were obtained to assess diastolic function. LV peak systolic global longitudinal strain was calculated using the automated functional imaging (AFI) strain technique (Fig 2). All studies were reviewed by pediatric cardiologists (B.H., N.A., D.C.) and a technician (C.P.) who were blinded to the patient exposure group.

Vascular images included cIMT of the left and right common carotid artery obtained using the GE machine (Fig 3), and PWV was calculated from measurements of pulse transit time (which were obtained using pulsed wave Doppler) and the distance (obtained manually using a measuring tape) travelled by the pulse between the carotid and femoral arteries.[16] This distance represented a direct distance of common carotid artery to femoral artery pulse multiplied by 0.8.[16] Transit time was indirectly obtained by subtracting time delay between the onset of R wave and upstroke of common carotid artery and onset of R wave and upstroke of common femoral artery. PWV was then calculated.[17]

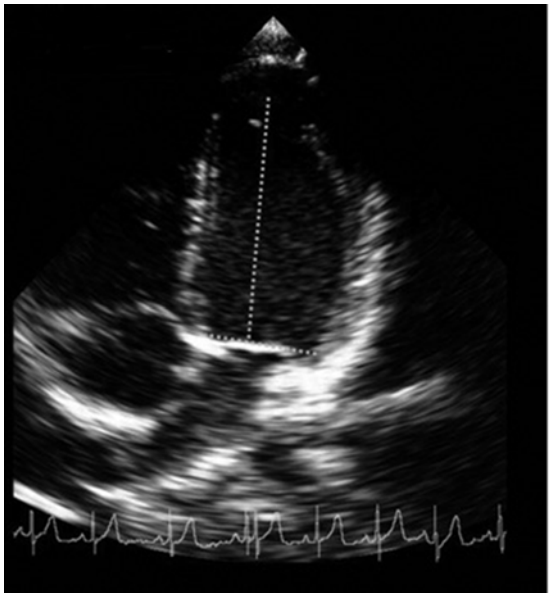

**Figure 1.** Measurement of sphericity index (in apical four chamber view)

Details regarding the echo protocol and vascular measurements are available in Appendix A.

Data were entered and analysed using SPSS version 20.0. Data were presented as mean – standard deviation, median and interquartile range, or percentages as appropriate. z-Scores were also calculated for echocardiographic data using a software that is freely available (http://zscore.chboston.org/).[17] Comparisons between the exposed and unexposed groups were log-transformed and adjusted for age, maternal BMI, gestational age at delivery, child's birth weight, child's BMI, and heart rate by multivariable linear regression analysis. A p-value <0.05 was used to determine statistical significance.

## Results

Anthropometric, echocardiographic, and vascular data were obtained from 136 study participants (68 in each cohort). Baseline characteristics such as age, birth weight, and current anthropometric data were similar across the study groups, with the exception of maternal BMI and gestational age at delivery (Table 1). Of the 68 study participants in the exposed group, 15 (22%) mothers had pre-gestational diabetes mellitus (8 type 1 diabetes mellitus mothers and 7 type 2 diabetes mellitus mothers), while the remaining 53 (78%) had gestational diabetes mellitus.

### *Cardiac outcomes*

Results of cardiac morphometry, systolic, diastolic and global function, as well as global longitudinal strain are presented in Table 2. Cardiac shape, including the relative wall thickness and left and right sphericity index, showed similar values between the two groups. There was no difference between the systolic and diastolic functional parameters between the exposed and unexposed groups (Table 2).

### *Vascular outcomes*

Results of vascular outcomes are shown in Table 3. The parameters of vascular assessment were statistically insignificant between children exposed to maternal hyperglycaemia as compared to controls.

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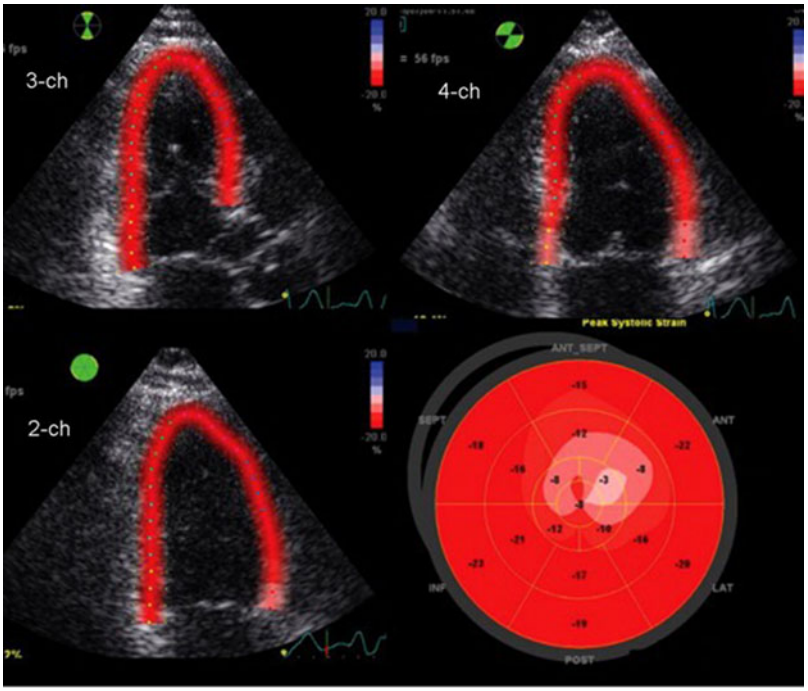


**Figure 2.** Gobal longitudinal strain from 2, 3 and 4 chamber view and Bull's eye measurement of regional strain

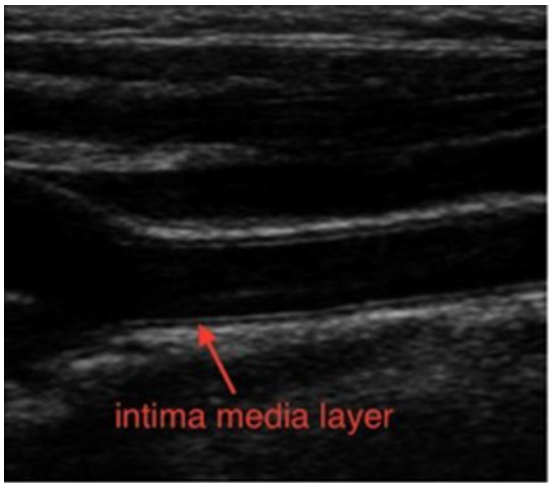


**Figure 3.** Ultrasound obtained carotid artry images for CIMT measurement

Interobserver variability of cIMT measurement was done in 32 randomly selected samples. Both the observers (i.e., Z.H. and C.P.) were unaware of the exposure status of the child. Bland–Altman plot was used to visualise the agreement that showed good agreement among the observers (ICC = 0.93, 95% CI = 0.857–0.964, $p < 0.0001$) (Fig 4).

Subgroup analysis was conducted to compare all the cardiac and vascular outcomes between the two groups. Firstly, there were no differences in cardiac and vascular outcomes in children born to mothers with pre-gestational as compared to gestational diabetes. Children who were born to mothers on medication (metformin and/or insulin) for blood sugar control had significantly lower mitral E/A ratio and E/A z-score as compared to those who were on dietary control. A further subgroup analysis was conducted between children of mothers who were on medications for hyperglycaemia as compared to controls. It was seen that cIMT was significantly higher in children whose mothers were on medication as compared to controls (median cIMT = 0.48 versus 0.46 mm, respectively, $p = 0.03$). However, it is important to note that the study was not initially powered for these; *post hoc* analysis reported power of <80% for all subgroup analyses.

## Discussion

In children between the ages of 2 and 5 years, there was no statistically significant difference seen in cardiac morphology, systolic and diastolic function, or vascular remodelling outcomes in those born to diabetic mothers compared to those born to non-diabetic women. This study is unique as it only included children who were appropriate for gestational age at birth. This is an important subgroup to study as it is the most common outcome in women with hyperglycaemia during pregnancy.

Cardiac morphological changes such as thickened interventricular septum (>4 mm) have been reported in 30% neonates of diabetic mothers with uncontrolled diabetes and who were macrosomic at birth.[18] However, they only included neonates of diabetic mothers without a control group as reference. Since extremes of birth weight (<2.5 or >4 kg) may have an effect on cardiac morphology, it is important to control for this confounder.[19] Also, since a majority of the children (80–90%) born to mothers are within the normal weight range of 2.5–4 kg, it is important to study the cardiovascular changes in the most common phenotype.[11] Our study only included appropriate-for-gestational-age babies so that the *in utero* insult of maternal hyperglycaemia could be studied independent of the effect of birth weight. This data indicates that children who are born to diabetic mothers and are appropriate for gestational age, may not be at high risk for future cardiovascular risk compared to the general population. This reflects an important finding for resource allocation for long-term management of children born to diabetic mothers.

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**Table 1.** Demographic and clinical characteristics of the study groups.

| Characteristics | Exposed group (n = 68), mean (95% CI) | Unexposed group (n = 68), mean (95% CI) | p-Value |
|---|---|---|---|
| Maternal age (years) | 30.8 ± 3.9 | 27.3 ± 4.2 | <0.001 |
| Maternal BMI (kg/m$^2$) | 27.67 (26.21–29.12) | 24.74 (23.73–25.75) | 0.02 |
| Management of hyperglycaemia, n (%) | | | |
| Dietary | 24 (35.8) | | |
| Oral meds | 25 (37.3) | | |
| Insulin | 18 (26.9) | N/A | – |
| Gestational age at delivery (weeks) | 38.5 ± 0.9 (38.2–38.7) | 38.9 ± 1.0 (38.6–39.2) | 0.009 |
| Birth weight (kg) | 3.2 (3.1–3.3) | 3.1 (3.0–3.2) | 0.52 |
| Child's age (years) | 3.8 (3.6–4) | 3.6 (3.4–3.8) | 0.16 |
| Current weight of child (kg) | 15.1 (14.3–15.8) | 14.6 (14.0–15.1) | 0.28 |
| Current height of child (cm) | 99.6 (97.9–101.3) | 98.4 (96.6–100.1) | 0.30 |
| Child's BMI (kg/m$^2$) | 15.1 (14.7–15.5) | 15.0 (14.7–15.2) | 0.73 |

BMI, body mass index.

Changes associated with hypertrophic cardiomyopathy (such as thickened ventricular septum and/or free walls) are known to resolve in infants of diabetic mothers within the first few months of life.[20] This finding may be the result of a transient hyperglycaemic insult *in utero* that may cause hyperplasia and hypertrophy of myocardial cells, which is resolved in early life,[9,21] but there is lack of literature looking at cardiac morphology in older children. Our study adds to the evidence that cardiac morphological differences were not seen in appropriate-for-gestational-age children aged 2–5 years with similar exposure as these fetuses were likely exposed to a controlled hyperglycaemic state.

Kozak-Barany et al. reported that neonates (aged 2–5 days) of diabetic mothers had longer mitral deceleration time compared to the unexposed group despite well-controlled glucose, while the rest of the systolic and diastolic parameters were insignificant.[9] This effect may be due to the exposure of maternal hyperglycaemia during the third trimester and subsequent fetal hyperinsulinemia leading to neonatal cardiac hypertrophy.[9] Decreased mitral E/A ratio and prolonged Tei index have also been reported in newborns of diabetic mothers; however, there was no correlation of this finding with maternal HbA1c.[10] Mehta et al. reported lower mitral E/A ratio at birth in children born to mothers with gestational diabetes, but this resolved by 2–4 weeks of age.[22] Zablah et al. also reported lower S′ and higher E/E′ ratios in neonates of diabetic mothers as compared to controls.[23] However, all these studies assessed children during the neonatal period but did not follow these changes in early childhood. None of the cardiac functional parameters were statistically significant in our study. This may suggest that by the age of 2–5 years, in those children who were born appropriate for gestational age, there is reversal of diastolic functional changes demonstrated in the literature in neonates of diabetic mothers.[9,10]

Assessment of strain and strain rate using two-dimensional speckle-tracking echocardiography is widely used to assess global cardiac function in the pediatric population.[24] Speckle tracking has the ability to quantify global and regional wall deformation independently from the angle of insonation.[25] Fetuses born to mothers with well-controlled gestational diabetes have been reported to have significantly decreased peak systolic myocardial strain in the apical segments of the interventricular septum as compared to controls.[26] Diastolic dysfunction in the LV and right ventricle (RV) have also been reported in fetuses of diabetic mothers.[27] Our work had contrary findings to Al-Biltagi et al. who demonstrated statistically significant reduced global longitudinal strain in neonates of diabetic mothers irrespective of glucose control,[10] suggesting that the changes in strain may have reversed by the age of 2–5 years. In the present study, LV global longitudinal strain was not statistically significant between the exposed and unexposed groups.

Children of diabetic mothers (7–16 years) were reported to have higher systolic blood pressure as compared to controls.[28,29] However, a large cohort study of 12,500 German children aged 3–17 years born to diabetic mothers concluded that gestational diabetes mellitus did not appear to have an effect on the systolic or diastolic blood pressure or the cholesterol levels of the child.[30] The present study had similar findings to Beyerlein et al. where there were no statistically significant differences in the blood pressures between the two groups.

cIMT has been evaluated as a non-invasive marker for subclinical atherosclerosis in both the adult and pediatric populations.[31] There is limited data available regarding the vascular assessment of children born to diabetic mothers. Atabek et al. demonstrated that there was no significant difference in the cIMT in neonates of diabetic mothers as compared to controls.[15] This study had a very small sample size and thus was heavily underpowered. The present study, despite being adequately powered, did not show a difference in cIMT between the two groups. Carotid-femoral PWV is established as a gold standard for measuring arterial stiffness in children,[32] but there is dearth of data on the effect of specific conditions such as exposure to maternal hyperglycaemia. We did not use Sphygmocor as it was not able to record data in this age group, and hence traditional measurement was used to calculate PWV. In the absence of these devices, measurements using B-mode ultrasonography have been used in adults as well as pediatric populations.[33,34] Neonates of mothers with uncontrolled hyperglycaemia (HbA1c ≥6%) during pregnancy had significantly higher PWV than neonates of unexposed mothers, but were not followed

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**Table 2.** Cardiac outcomes of the study groups.

| Characteristics | Exposed group (n = 68), median (interquartile range) | Unexposed group (n = 68), median (interquartile range) | β, 95% CI | Adjusted p value |
|---|---|---|---|---|
| Cardiac morphometry | | | | |
| LV base-apex length (cm) | 5.1 (4.9–5.4) | 5.0 (4.8–5.3) | 0.07 (−0.08, 0.2) | 0.41 |
| LV basal diameter (cm) | 1.9 (1.7–2.0) | 1.8 (1.7–2.0) | 0.1 (−0.05, 0.14) | 0.33 |
| LV sphericity index | 2.7 (2.5–3.0) | 2.8 (2.6–2.9) | −0.01 (−0.1, 0.1) | 0.94 |
| LV mass (g) | 25.7 (20.4–31.7) | 24.2 (18.8–28.0) | −0.02 (−4.4, 3.7) | 0.85 |
| z-Score | −1.3 (−2.0 to −0.3) | −1.3 (−2.0 to −0.6) | −0.05 (−0.6, 0.4) | 0.63 |
| RV base-apex length (cm) | 4.5 (4.1–4.9) | 4.5 (4.3–4.9) | −0.02 (−0.2, 0.2) | 0.83 |
| RV basal diameter (cm) | 1.7 (1.6–1.8) | 1.7 (1.6–1.9) | −0.09 (−0.1, 0.05) | 0.42 |
| RV sphericity index | 2.5 (2.4–2.8) | 2.6 (2.4–2.8) | 0.04 (−0.1, 0.1) | 0.74 |
| LA area ($cm^2$) | 5.6 (5.1–6.4) | 5.4 (4.7–6.2) | 0.04 (−0.3, 0.5) | 0.65 |
| Interventricular septum (cm) | 0.4 (0.4–0.5) | 0.4 (0.4–0.5) | 0.08 (−0.02, 0.04) | 0.45 |
| z-Score | −2.6 (−2.8 to −1.5) | −2.5 (−2.8 to −2.1) | 0.06 (−0.5, 0.8) | 0.58 |
| Left posterior wall (cm) | 0.4 (0.4–0.42) | 0.4 (0.4–0.41) | 0.07 (−0.02, 0.03) | 0.53 |
| z-Score | −2.0 (−2.4 to −1.6) | −1.9 (−2.3 to −1.3) | 0.03 (−0.4, 0.5) | 0.82 |
| LV end-diastolic diameter (cm) | 3.0 (2.6–3.2) | 3.1 (2.7–3.3) | −0.16 (−0.3, 0.06) | 0.16 |
| Relative wall thickness | 0.3 (0.25–0.33) | 0.3 (0.23–0.3) | 0.08 (−0.02, 0.04) | 0.52 |
| Systolic function | | | | |
| LV EDV (ml) | 36.6 (32.8–42.1) | 36.5 (30.9–43.1) | −0.06 (−3.8, 1.7) | 0.45 |
| z-Score | −0.4 (−0.8–0.2) | −0.4 (−0.9–0.4) | −0.04 (−0.6, 0.4) | 0.61 |
| LV ESV (ml) | 12.6 (10.5–14.9) | 12.4 (10.4–14.3) | 0.03 (−0.9, 1.2) | 0.72 |
| z-Score | −0.1 (−0.6–0.6) | −0.2 (−0.6–0.2) | 0.07 (−0.2, 0.5) | 0.54 |
| Ejection fraction (%) | 65 (62–68) | 66.1 (64–68.7) | −0.1 (−3.1, 1.1) | 0.34 |
| z-Score | 0.3 (−0.3–0.9) | 0.5 (0.1–1.0) | −0.16 (−0.6,0.2) | 0.18 |
| Stroke volume (ml) | 23.9 (20.3–28.1) | 24.1 (20.9–28.9) | −0.08 (−3.4, 1.2) | 0.36 |
| z-Score | −0.4 (−0.8–0.6) | 0.0 (−0.8–0.8) | −0.08 (−0.6, 0.2) | 0.45 |
| Cardiac index ($L/min/m^2$) | 4.2 (3.3–5.2) | 4.0 (3.8–4.2) | −0.07 (−0.09, 0.05) | 0.51 |
| RV FAC (%) | 36.9 (30.7–41.7) | 38.5 (32.6–43.2) | −0.12 (−4.4, 1.8) | 0.41 |
| VCFc/ESWS z-score | 0.25 (−0.6–1.3) | 0.4 (−0.7–1.3) | −0.11 (−0.9, 0.3) | 0.35 |
| MAPSE | 13 (11–14) | 13 (12–13) | −0.12 (−1.1, 0.3) | 0.27 |
| TAPSE | 19 (17–20) | 19 (17–20) | −0.02 (−1.1, 1.2) | 0.89 |
| z-Score | 0.8 (−0.4–2.2) | 0.9 (−0.2–1.8) | 0.14 (−0.3, 1.2) | 0.23 |
| Tricuspid lateral S′ (cm/s) | 0.12 (0.11–0.13) | 0.12 (0.11–0.13) | 0.15 (−0.002, 0.01) | 0.18 |
| Diastolic function | | | | |
| Mitral E-wave (cm/s) | 1.0 (0.9–1.1) | 0.99 (0.89–1.1) | 0.11 (−0.03, 0.09) | 0.36 |
| Mitral A-wave (cm/s) | 0.6 (0.5–0.7) | 0.62 (0.53–0.7) | −0.04 (−0.06, 0.04) | 0.71 |
| Mitral E/A ratio | 1.6 (1.5–1.8) | 1.6 (1.4–1.8) | 0.08 (−0.07, 0.16) | 0.47 |
| z-Score | −0.6 (−0.8 to −0.3) | −0.5 (−0.9 to −0.2) | 0.06 (−0.13, 0.25) | 0.56 |
| Mitral DT (ms) | 133.3 (123.6–137) | 133.5 (122.9–143) | −0.16 (−19.9, 6.9) | 0.34 |
| z-Score | 0.5 (0.1–0.7) | 0.56 (0.2–1.0) | −0.14 (−0.6, 0.2) | 0.39 |
| Mitral lateral E′ (cm/s) | 0.14 (0.12–0.15) | 0.14 (0.12–0.16) | −0.11(−0.02, 0.01) | 0.28 |
| Mitral septal E′ (cm/s) | 0.12 (0.1–0.13) | 0.12 (0.11–0.13) | 0.02 (−0.007, 0.01) | 0.84 |
| Mitral septal E/E′ | 8.4 (7.4–9.1) | 8.5 (7.4–9.4) | 0.08 (−0.4, 0.9) | 0.92 |

(*Continued*)

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**Table 2.** (*Continued*)

| Characteristics | Exposed group (n = 68), median (interquartile range) | Unexposed group (n = 68), median (interquartile range) | β, 95% CI | Adjusted p value |
|---|---|---|---|---|
| Global function | | | | |
| IVCT (ms) | 44.1 (41.0–48.4) | 44.3 (40.3–50.3) | −0.13 (−7.6, 1.9) | 0.24 |
| IVRT (ms) | 45.6 (41.1–49.8) | 45.0 (39.0–51.1) | −0.05 (−4.9, 3.0) | 0.64 |
| Ejection time (ms) | 244.9 (228.2–258.5) | 243.3 (231.7–254) | −0.03 (−13.6, 9.4) | 0.73 |
| Tei index | 0.37 (0.33–0.39) | 0.36 (0.34–0.40) | −0.11 (−0.03, 0.01) | 0.32 |
| z-Score | −0.02 (−0.3–0.2) | −0.1 (−0.26–0.24) | −0.1 (−0.2, 0.1) | 0.34 |
| Global longitudinal strain (%) | −23.8 (−24.8 to −22.2) | −23.2 (−24.8–21.6) | −0.008 (−1.7, 1.6) | 0.94 |

LA, left atrium; LV, left ventricle; RV, right ventricle, FAC, fractional area change; EDV, end-diastolic volume; ESV, end-systolic volume; VCFc, velocity of circumferential fibre shortening (corrected); ESWS, end-systolic wall stress; DT, deceleration time; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time.
p-Value was obtained through log-transformation of all variables and multivariable linear regression and was adjusted for child's age, maternal BMI, gestational age at delivery, child's birth weight, child's BMI, and heart rate.

**Table 3.** Vascular outcomes of the study groups.

| Characteristics | Exposed group (n = 68), median (interquartile range) | Unexposed group (n = 68), median (interquartile range) | β, 95% CI | Adjusted p value |
|---|---|---|---|---|
| Systolic BP (mmHg),<br>z score | 105.7 (99.2–112.8)<br>1.1 (0.3–1.9) | 106.0 (99.0–113.1)<br>1 (0.63–2.0) | −0.02 (−0.03,0.2)<br>0.05 (−0.4,0.6) | 0.87<br>0.67 |
| Diastolic BP (mmHg),<br>z score | 63.2 (57.0–69.6)<br>1.2 (0.7–2.1) | 60.2 (56.9–65.5)<br>1.2 (0.6–2.0) | 0.18 (−0.6,6.2)<br>0.16 (−0.15,0.8) | 0.10<br>0.18 |
| Right cIMT (mm) | 0.47 (0.45–0.51) | 0.47 (0.43–0.49) | 0.17 (−0.008,0.04) | 0.18 |
| Left cIMT (mm) | 0.47 (0.43–0.51) | 0.46 (0.44–0.50) | 0.11 (−0.01,0.03) | 0.33 |
| PWV (cm/s) | 4.5 (4.0–5.0) | 4.5 (4.2–4.9) | −0.02 (−0.4,0.4) | 0.89 |

BP, blood pressure; cIMT, carotid intima media thickness; PWV, pulse wave velocity.
p-Value was obtained through log-transformation of all variables and multivariable linear regression and was adjusted for child's age, maternal BMI, gestational age at delivery, child's birth weight, child's BMI, and heart rate.

up later in life.[35] The present study reported no difference in this vascular parameter between the two groups. One plausible explanation for this difference may be that hyperglycaemia, which increases serum insulin-like growth factors 1 and 2, may cause proliferation of vascular smooth muscle and hence lead to increased arterial stiffness.[36] However, depending on glycaemic control during pregnancy, macrovascular changes may reverse (as seen in our work).

We also did subgroup analysis to assess the difference between children exposed to mothers with pre-gestational diabetes mellitus as compared to those who have gestational diabetes mellitus. There was no difference between the cardiovascular parameters between the two groups. Our study reported decreased E/A ratio in children whose mothers were on medications to control their blood sugars as compared to those on dietary control. As we did not have adequate documentation regarding glucose control during pregnancy, the use of medications acted as a surrogate for inadequate control. It may be then plausible to hypothesise that those who were on medications had transient but higher exposure to uncontrolled blood sugars, which may affect the diastolic function of the heart. This finding is contradictory to Rijpert et al. who reported that cardiac function at 8 years of age in children of women with type 1 diabetes is not different from that of controls.[37] Further subgroup analysis reported that cIMT was significantly higher in children whose mothers were on medications for blood sugar as compared to controls. Chen et al. reported that PWV was increased in neonates whose mothers had uncontrolled hyperglycaemia (HbA1c ≥6%).[35] This finding suggests that vascular function in this subgroup may be affected *in utero* and hence cause increased cIMT as seen in early childhood. As the subgroup analysis was not the main aim of the study, it contained a small sample of children. Further work with larger cohorts would be required to validate these findings.

There are several strengths and limitations in this study. A detailed analysis of all cardiac parameters was conducted in this study. z-Scores were also calculated for all available cardiac parameters and compared for both groups. This has the advantage of comparing various parameters against available pediatric normative data, hence adding to the robustness of the data presented. There are a few limitations in this study. There is no standard procedure of monitoring and documenting glucose control during pregnancy at our centre. Hence we were not able to comment on this parameter. One of the shortcomings of our study was that it was not designed to study vascular changes in pre-gestational diabetes mellitus of newborns who were small or large for gestational age. It would be important to follow these three groups (i.e., appropriate, small, and large for gestational age) longitudinally to compare the cardiac and vascular changes. Further, as the subgroup analysis was not a part of the initial objectives of this study, it was not adequately powered to draw conclusions. The present study only looked at macrovascular assessment (done in a non-fasting state), while microvascular assessment using techniques such as flow-mediated dilatation was not performed.

In conclusion, the present study indicates that children 2–5 years of age who were born appropriate for gestational age at term to mothers with hyperglycaemia during pregnancy had no

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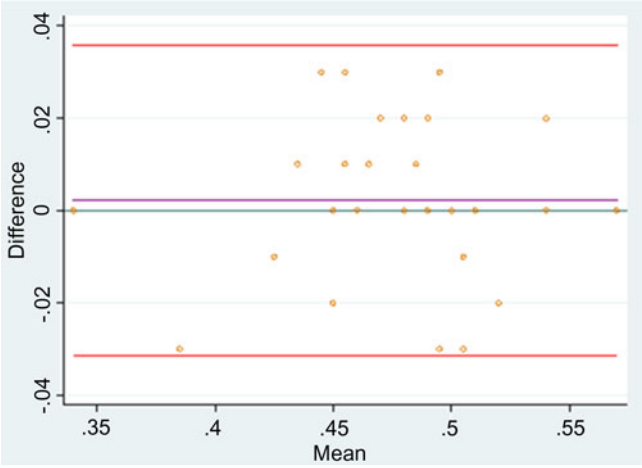


**Figure 4.** Bland-Altman plot to assess inter-observer variability

difference in cardiac and vascular outcomes as compared to controls. However, decreased mitral E/A ratio and increased cIMT were seen in children of mothers who had suboptimal glucose control during pregnancy, thus indicating that cardiac and vascular changes may be present in this subgroup. We cannot comment on the cardiac status at birth as the study was not designed as a longitudinal study. Future work requires longitudinal follow-up evaluating children of diabetic mothers (with robust measures of controlled and uncontrolled hyperglycaemia) from fetal stage to adulthood to help validate this hypothesis and design preventive programs for children of diabetic mothers who may be at a higher risk of future cardiovascular events.

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**Conflicts of Interest.** None.

**Ethical Standards.** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (National Bioethics Committee, Pakistan) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (Ethics Review Committee, The Aga Khan University).

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## Appendix A: Echocardiography and vascular assessment protocol

For detailed cardiac evaluation, the following parameters were analysed:

*Cardiac morphometry:* Linear measurements of base-to-apex length and basal diameter of LV and RV were determined from an apical four-chamber view at end-diastole. Sphericity index (base to apex length/basal diameter of the ventricle) for both the ventricles was then calculated. LV end-diastolic septal and posterior wall thicknesses were measured in parasternal long-axis view. Relative wall thickness was calculated as (posterior + septal wall thickness/LV end-diastolic diameter). We also assessed LV mass using (5/6 × area × length), which was validated, and z-scores on LV mass were determined based on body surface area. LA area was assessed in the apical four-chamber view at end-systole and indexed to body surface area.

*Systolic function:* Measurements for the LV included EF, shortening fraction, stroke volume, heart rate, cardiac output (measured in parasternal long- and short-axis view), and MAPSE (measured by M-mode in apical four-chamber view). For the RV, this included TAPSE measured by M-mode and systolic annular peak velocity (S′) using TDI. LV EF and volumes were obtained from apical four-chamber and parasternal short-axis views using the area length method. RV function was assessed using fractional area of change.

VCFc is a preload-independent measure of LV function and is inversely related to end-systolic stress. It was calculated using the formula (shortening fraction/heart rate-adjusted ejection time). For shortening fraction, we used the formula (end-diastolic diameter − end-systolic diameter/end-diastolic diameter). These diameters were assessed in parasternal short-axis view.

*Diastolic function:* Using PWD, mitral inflow peak early filling (E) and peak atrial filling (A) wave velocities were measured using the apical four-chamber view, and E/A ratio was calculated. Deceleration time was measured as the time between peak E velocity and the point where the velocity returns to zero. TDI-derived peak early (E′) and peak late (A′) diastolic velocities were also measured at the base of the interventricular septum. E-wave to LV E′ velocity ratio (E/E′) was then calculated.

*Global function:* The myocardial performance index (Tei index) has been used to assess combined LV systolic and diastolic function. It is calculated as (isovolumic contraction time + isovolumic relaxation time/ejection time). These timings were reported separately and also as a collection function in the form of Tei index value. Each value was recorded over three consecutive beats and averaged out for calculation of the index. It was measured using a PWD positioned at the tip of mitral leaflets in the apical five-chamber view.

*Strain analysis:* Digital loops with three consecutive cardiac cycles were acquired from apical two, three, and four-chamber views, with frame rate set at >60 frames/second (frame rate to heart rate ratio of close to 1). Strain analysis, via speckle tracking, was performed directly on the system for each of the three apical views. The operator manually identified two points on each side of the mitral valve and one point at the LV apex. Using the AFI strain technique, the software automatically detects the endocardium and tracks the myocardium during the entire cardiac cycle. U-shaped regions of interest that encompass the basal, mid, and apical segments of the LV are then created. Global longitudinal strain is then calculated by averaging the 16 segment strains of the LV. Tracking quality is assessed by the observer, and endocardial tracing is readjusted or the imaging repeated if the quality is unsatisfactory.

For vascular evaluation, the following parameters were analysed:

*cIMT:* The examination was performed using the Association for European Pediatric Cardiology Working Group on Cardiovascular Prevention guidelines. The GE Healthcare Vivid E9 ultrasound scanner with a 7–12 MHz linear transducer was used to acquire the images. The subject was placed supine in a quiet room with the head extended and turned away from the transducer. Longitudinal images of the common carotid artery (both sides) were obtained proximal to the carotid bulb. Minimum five-second clips were recorded and stored for each vessel to allow selection of the most appropriate frame for offline analysis. cIMT measurements were taken from the far wall of the common carotid artery, 10 mm away from the carotid bulb. On the carotid wall, two bright lines separated by a darker area were identified. The IMT software was used to delineate 105–110 points on a pixel basis, and the average cIMT value (over three consecutive heart cycles) was calculated for each side.

*PWV:* Carotid femoral PWV was calculated by dividing distance travelled by the transit time. The study participant was laid supine with the head extended. The right carotid and right femoral artery were felt manually, and PWD was obtained on each. The distance signified the direct distance of common carotid artery to femoral artery pulse multiplied by 0.8. Transit time was indirectly obtained by subtracting time delay between the onset of R-wave and upstroke of common carotid artery and onset of R-wave and upstroke of common femoral artery. PWV was then calculated.

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