Indian Heart Journal 72 (2020) 576–581

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Fetal echocardiography at term in diabetic pregnancies helps predict the adverse neonatal outcome - Results of a prospective observational study from South India

Grandhi Mrudhula Tejaswi [a], Jyothi Samanth [b], Akhila Vasudeva [a, *, 1], Leslie Lewis [c], Pratap Kumar [a], Krishnananda Nayak [b], R. Padmakumar [d]

[a] Department of Obstetrics and Gynecology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India
[b] Department of Cardiovascular Technology, Manipal College of Health Professions, Manipal Academy of Higher Education, Manipal, Karnataka, India
[c] Department of Pediatrics, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India
[d] Department of Cardiology, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India

ARTICLE INFO

Article history:
Received 26 December 2019
Accepted 29 September 2020
Available online 6 October 2020

Keywords:
Gestational diabetes mellitus
Fetal echocardiography
Fetal hypertrophic cardiomyopathy
Tissue Doppler imaging

ABSTRACT

There is sparse Indian data on whether fetal echocardiography among pregnant diabetics would be useful to predict adverse perinatal/neonatal outcome.

Objectives: To study fetal cardiac changes in diabetic mothers and non-diabetic controls from 24 weeks gestation until the neonatal period; correlate them with maternal glycemic control; study their implications on adverse perinatal/neonatal outcome.

Methodology: Prospective observational cohort study. Pregnant diabetics (17 overt, 66 gestational) recruited beyond 24 weeks, divided as well (39) and poorly (44) controlled, based on American Diabetes Association 2016 criteria. Controls were 102 healthy non-diabetic pregnancies. Fetal echocardiography performed at weeks 24–32, 32–36, >37, and between 4 and 7 days on neonates. The thickness of Interventricular septum (IVS), Right Ventricle (RV), and Left ventricle (LV) assessed with M mode. E/A ratio across Tricuspid/Mitral valves and Tei index determined. TDI(Tissue Doppler imaging) used to assess tissue annular velocities across IVS, RV, and LV. Maternal glycemic control and various perinatal/neonatal adverse outcomes were recorded.

Results: Significant myocardial hypertrophy seen among fetuses of diabetic mothers versus controls, most severe at term among the poorly controlled diabetics. Structural changes persisted in the neonate. At term, fetal myocardial dysfunction was evident among diabetic pregnancies only as poor annular systolic velocity across IVS, RV using TDI. However, Tissue Doppler changes could not predict adverse perinatal/neonatal outcome. Myocardial dysfunction could not be demonstrated in the neonates. Myocardial hypertrophy at term was a surrogate marker for suboptimal glycemic control, and it could predict important neonatal morbidities like hypoglycaemia, hyperbilirubinemia, prolonged NICU stays, and persistent foetal cardiac shunts.

Conclusion: Our study shows a significant association between fetal myocardial hypertrophy and maternal glycemic control among GDM pregnancies. There also seems to be an association between fetal myocardial hypertrophy and some of the adverse perinatal events including hypoglycemia. However these newborns were not found to have clinically relevant cardiac comorbidities even though there was significant septal hypertrophy in utero.

© 2020 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

* Corresponding author.
E-mail addresses: tejaswigrandhi92@gmail.com (G. Mrudhula Tejaswi), jyothisamanth@ymail.com (J. Samanth), Akhila.vasudeva@manipal.edu, akhilavasudeva@gmail.com (A. Vasudeva), lelsielewis1@gmail.com (L. Lewis), Pratap.kumar@manipal.edu (P. Kumar), krishnayak2008@gmail.com (K. Nayak), Padmakumar69@yahoo.co.in (R. Padmakumar).
[1] Postal address of correspondence: Department of obstetrics and gynecology, Kasturba medical college, Manipal Academy of higher education, Manipal, Udupi Tq and dist; Karnataka, India, 576104.

https://doi.org/10.1016/j.ihj.2020.09.017
0019-4832/© 2020 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

Diabetes mellitus is the most common metabolic disorder complicating pregnancy. International Diabetes Federation estimates that 16.2% of women with live births had hyperglycemia in pregnancy.[1] Gestational Diabetes Mellitus (GDM) contributed to 85%. Diabetes is a major health problem in India, with prevalence rates reported 4.6%–14% in urban, and 1.7%–13.2% in rural areas.[2] Neonates born to diabetic mothers are at risk of cardiovascular problems due to structural cardiac defect, myocardial hypertrophy, or impaired cardiac function.[3] Fetal echocardiography is a non-invasive screening tool for assessment of myocardial structure and function. Tissue Doppler imaging (TDI) is a recent method of studying functional changes in the heart, which is less dependent on flow dynamics and heart rate. Foetal myocardial changes in diabetic pregnancy are fairly understood. However, it is unclear whether these lead on to any significant persistent neonatal cardiac dysfunction. It is also unclear, whether studying foetal cardiac changes in pregnancy helps us predict adverse perinatal/neonatal outcome. In this study, cardiac structural and functional changes were assessed in foetuses of diabetic mothers and non-diabetic controls from 24 weeks onwards, until term pregnancy. Echo was performed in the neonatal period as well. We attempted to correlate foetal cardiac structural and functional changes to maternal glycemic control, and their implications on perinatal/neonatal outcome.

2. Methodology

This was a prospective observational cohort study carried out at the departments of obstetrics, neonatology and Cardiology, over two years from August 2016–August 2018. Institutional Ethics Committee approval was obtained ((IEC-467/2016). Of the 200 women recruited, 11 were lost to follow up, and fetal echo was suboptimal in 4 patients due to inadequate acoustic window. Finally, 185 pregnant women were studied, which included 102 controls and 83 cases, all being booked cases and delivered at our hospital. Cases included 17 overt (pregestational) diabetes and 66 GDM as per the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria. Cases were managed with Medical Nutrition Therapy (MNT), exercise, with or without Oral Hypoglycemics (OHA)/Insulin as per standard clinical protocols. Pregnant diabetics were regularly monitored with fasting (FBS) and 2-h Postprandial blood sugars (PPBS). All the DM cases were divided into well controlled (39) and poorly controlled (44) DM based on the American Diabetic Association (ADA) criteria 2016, taking their FBS/PPBS values within a week of first fetal echocardiographic scan done between 24 and 32 weeks of gestation. This classification was not dynamic. Patients remained in their respective original groups throughout the analysis disregarding the 3 cross overs. Hundred and Two healthy euglycemic pregnant women were taken as controls. Women with pre-existing hypertension, gestational hypertension, renal disease, liver disease, hematologic diseases, maternal cardiac diseases, evidence of congenital foetal anomaly (including cardiac), intrauterine growth restriction, chromosomal abnormalities, multiple pregnancies, foetal arrhythmia were excluded. Foetal echocardiography was performed by either a foetal medicine specialist or a trained cardiovascular technologist. We used Vivid 7 Echo machine (GE healthcare system) with a linear convex probe of 3–4 MHz frequency. Serial Fetal echoes were performed on all the participants at three gestational period windows: 24–32 weeks, 32–36 weeks, > 37 weeks and in the neonates between 4 and 7 days of life.

Cardiac structure and function were assessed using 2D, M-mode, Conventional Doppler and Tissue Doppler imaging. M-mode (Fig. 1a) was obtained perpendicular to the ventricular long axis in 4 chambered view of the heart, to assess myocardial thickness. The mitral and tricuspid inflow velocities at early (E) and late (A) diastole were recorded from the apical four-chamber view with pulsed wave Doppler sampling volume positioned at tips of the mitral valve (MV) and tricuspid valve (TV) respectively. Tei index also known as myocardial performance index (MPI) of left and right ventricle was measured using respective atrioventricular valve and semilunar valve Doppler tracings.

TDI (Fig. 1b) was performed in the 4 chambered view of heart to study annular tissue velocities from interventricular septum (IVS) annulus, left ventricle (LV) and right ventricle (RV) free wall annulus. TDI included systolic (S), early diastolic (Em) and late diastolic (Am) velocities.

We studied the following perinatal/neonatal outcomes - macrosomia, cardiotocography (CTG) changes requiring delivery, perinatal asphyxia, neonatal hypoglycemia, neonatal hyperbilirubinemia, prolonged NICU stay > 7 days, Apgar score < 7 at 5 min, respiratory distress syndrome, subtle cardiac abnormalities diagnosed at birth (small atrial/ventricular septal defect) and persistent fetal shunts (Patent ductus arteriosus, patent foramen ovale) diagnosed in the neonate. Statistical analysis was performed using one-way analysis of variance (ANOVA), Chi-square test and multivariate analysis. Inter observer variability was tested in a sample of 20 cases which showed good agreement between the two observers with an intra-class correlation of 0.990 (95% CI of 0.975 and 0.996) for Septal thickness, 0.991 (95% CI of 0.978 and 0.996) for RV Tei index and 0.994 (95% CI of 0.959 and 0.998) for RV systolic tissue annular velocity.

3. Results

Mean FBS and 2 h PPBS values among diabetics at three gestational periods are shown in Table 1. All Diabetic women were on MNT. Besides, out of the 39 in the well-controlled group, 8 (20%) were on OHA, and one woman was on Insulin. Out of the 44 in the poorly controlled group, 13 (29%) were on OHA, 8 (18%) on Insulin, and 9 (20%) were on a combination of OHA + Insulin. In the poorly-controlled group, mean sugar values were not very high, rather only 10–30 mg/dl above the strict ADA criteria. Thus our "poorly-controlled" group does not reflect women with very high uncontrolled sugars being non-compliant to management. This group instead reflects a large majority of GDM women being managed with MNT + medications from the time of diagnosis in the second trimester, with borderline sugar control. These women were on regular follow up with obstetricians + physicians and were compliant with treatment. Structural and functional parameters among 3 groups have been compared using ANOVA test with Boneferroni correction for sub group analysis (Tables 2, 3).

3.1. Structural changes

Foetal myocardial hypertrophy (Table 2) was evident as early as 24–32 weeks among the poorly-controlled group. By 32–37 weeks, they were evident among both well and poorly-controlled groups. At term, myocardial hypertrophy was found to be associated with glycemic control status. For example, there were 35 fetuses with end-diastolic IVS thickness of >90th centile at term. Of the 35, majority (32) belonged to the poorly controlled diabetic group. Only one was in well-controlled diabetic group, and 2 in the non-diabetic control group. Structural changes were persistent in the neonate. On plotting a longitudinal data for IVS, RV and LV thickness (Fig. 2), we noticed a gradual myocardial thickening which plateaued between 32 and 37 weeks among the well-controlled

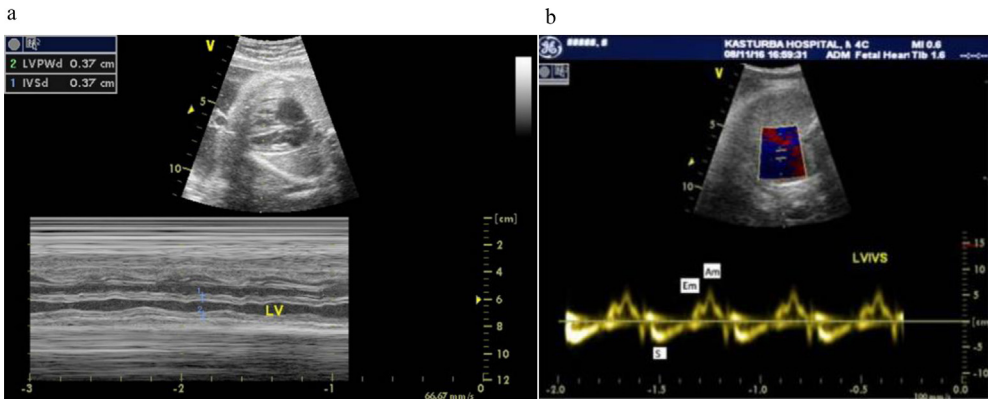

Fig. 1. a.)M-mode across LV and RV adjacent to AV valves; the measurement displays Inter ventricular thickness in diastole and LV wall thickness in diastole. b.)Tissue Doppler imaging; Em: Early diastolic tissue annular velocity; Am: Late diastole tissue annular velocity during atrial contraction phase; S: systolic tissue annular velocity.

Table 1
Mean FBS and 2 h PPBS values among diabetics in 3 gestations.

Gestational age	Well controlled diabetics (N=39)		Poorly controlled diabetics (N=44)	
	FBS (Mean ± SD)	2hr PPBS (Mean ± SD)	FBS (Mean ± SD)	2hr PPBS (Mean ± SD)
24–32 weeks	104.54 ± 7.38	158.26 ± 18.54	116.23 ± 7.21	159.72 ± 13.69
32–37 weeks	85.24 ± 7.43	107.23 ± 12.39	106.43 ± 5.29	158.23 ± 13.98
>37 weeks	83.95 ± 7.22	104.74 ± 11.11	96.44 ± 11.69	131.67 ± 21.64

FBS: fasting blood sugar value.
PPBS: Postprandial blood sugar value.

Table 2
Structural changes in all the 3 groups at different gestations.

Gestational age	Variables	Non diabetics (N=102)	Well controlled diabetics (N=39)	Poorly controlled diabetics (N=44)	Anova P value
		Mean ± SD	Mean ± SD	Mean ± SD	
24–32 weeks	EFW(grams)	1191.91 ± 421.18	1099.26 ± 556.29	1045.51 ± 557.92	0.269
	IVSD (mm)	4.18 ± 1.02	4.29 ± 0.63	4.29 ± 0.96	0.221
	LV D (mm)	4.12 ± 2.8	3.66 ± 0.59	3.94 ± 0.94	0.626
	RV D (mm)	3.77 ± 0.65	3.69 ± 0.85	4.63 ± 1.33*^	<0.001
32–37 weeks	EFW(grams)	2522.88 ± 588.52	2153.00 ± 536.79	2168.70 ± 632.79	0.557
	IVSD (mm)	4.07 ± 0.57	5.37 ± 1.2*	5.14 ± 1.6*	<0.001
	LV D (mm)	3.97 ± 0.52	5.7 ± 0.93*	4.8 ± 0.89*^	<0.001
	RV D (mm)	3.57 ± 0.92	4.93 ± 0.65*	4.59 ± 0.77*	<0.001
>37 weeks	EFW(grams)	2712.20 ± 292.59	2812.28 ± 425.73	2942.87 ± 424.203	0.071
	IVSD (mm)	4.97 ± 0.82	5.69 ± 0.72*	6.16 ± 1.10*^	<0.001
	LV D (mm)	4.39 ± 0.66	4.84 ± 1.21*	5.05 ± 0.94*	<0.001
	RV D (mm)	4.55 ± 1.04	4.95 ± 0.65*	5.50 ± 0.81*^	<0.001
Neonates between 4–7 days	Birth weight (grams)	2851.94 ± 445.71	2956.05 ± 473.14	2866.12 ± 594.49	0.488
	IVSD (mm)	4.26 ± 0.6	5.68 ± 0.4*	5.20 ± 0.73*	<0.001
	LV D (mm)	3.46 ± 0.57	4.43 ± 1.01*	3.65 ± 0.60^	<0.001
	RV D (mm)	3.55 ± 0.55	3.98 ± 0.81	4.89 ± 0.54*	<0.001

*: $p < 0.05$ vs Non Diabetic; ^: $p < 0.05$ vs well controlled; EFW: Estimated fetal weight; IVSD: IVS thickness at end diastole; LV D: LV thickness at end diastole; RV D: RV thickness at end diastole.

group. In the poorly controlled group, myocardial and septal hypertrophy continued to worsen till delivery.

3.2. Functional changes

As seen in Table 3, among foetuses of diabetic women, there was no consistent pattern of myocardial dysfunction using Conventional Doppler, throughout gestation as well as in the neonatal period. The fetal IVS and RV systolic tissue annular velocities were lower in diabetics at term gestation, but significantly higher than non - diabetics in the early neonatal period. We could not demonstrate an association between left ventricular systolic function and glycemic control status, in fact there is statistically insignificant increase in left ventricular systolic annular velocity among fetuses of diabetic women compared to non-diabetic control. Hence, poor glycemic control did not necessarily lead to poor myocardial function. Diastolic dysfunction was not evident. There were no significant cardiac functional impairments in neonates of diabetic mothers.

3.3. Implications of foetal cardiac changes on perinatal and neonatal morbidity

It is of interest to know if perinatal problems could be predicted based on fetal cardiac changes at term. We compared foetuses with septal thickness >90th centile to those with <90th centile, with

Table 3
Functional changes seen at term and neonates.

Gestational age	Variables	Non diabetics (N = 102)	Well ntrolled diabetics (N = 39)	Poorly controlled diabetics (N=44)	Anova P value
		Mean ± SD	Mean ± SD	Mean ± SD	
>37 weeks	MV E/A	0.83 ± 0.07	0.84 ± 0.16	0.91 ± 0.06	0.477
	TV E/A	0.81 ± 0.08	0.83 ± 0.07	0.77 ± 0.05	0.198
	LV TEI	0.58 ± 0.13	0.36 ± 0.06*	0.30 ± 0.04*	<0.001
	RV TEI	0.37 ± 0.05	0.35 ± 0.05	0.39 ± 0.10	0.82
	IVS Sm (cm/s)	5.52 ± 0.63	4.98 ± 0.85*	4.8 ± 0.60*	<0.001
	LV Sm (cm/s)	5.39 ± 0.35	5.9 ± 0.56	6.00 ± 0.57	0.16
	RV S (cm/s)	7.66 ± 1.16	6.10 ± 1.18*	4.92 ± 0.079*^	<0.001
	IVS Em/Am	0.85 ± 0.39	0.79 ± 0.24	0.73 ± 0.25	0.452
	LV Em/Am	0.88 ± 0.13	0.95 ± 0.18	1.02 ± 0.19	0.06
	RV Em/Am	0.69 ± 0.08	0.71 ± 0.12	0.68 ± 0.11	0.33
Neonates between 4–7 days	MV E/A	0.99 ± 0.15	1.01 ± 0.18	1.08 ± 0.01	0.74
	TV E/A	0.77 ± 0.06	0.89 ± 0.11*	0.84 ± 0.09	<0.001
	LV TEI	0.32 ± 0.1	0.38 ± 0.18	0.29 ± 0.12	0.131
	RV TEI	0.29 ± 0.06	0.29 ± 0.10	0.24 ± 0.08	0.08
	IVS Sm (cm/s)	4.27 ± 0.84	4.87 ± 1.11*	5.10 ± 1.98*^	<0.001
	LV Sm (cm/s)	4.83 ± 0.98	5.19 ± 0.97	5.35 ± 1.02*	<0.01
	RV Sm (cm/s)	6.18 ± 1.42	6.67 ± 1.58*	7.44 ± 1.94*^	<0.001
	IVS Em/Am	1.07 ± 0.32	0.95 ± 0.31	0.96 ± 0.26	0.94
	LV Em/Am	0.94 ± 0.31	0.92 ± 0.35	1.01 ± 0.46	0.34
	RV Em/Am	0.67 ± 0.15	0.81 ± 0.24*	0.72 ± 0.24*^	<0.001

*: p < 0.05 vs Non Diabetic, ^: p < 0.05 vs well controlled diabetics; MV E/A: Mitral valve Early diastolic wave/Atrial contraction wave ratio; TV E/A: Tricuspid Early diastolic wave/Atrial contraction wave ratio; RV TEI: Right ventricle Tei index; LV TEI: Left ventricle Tei index; TDI derived systolic(Sm) and diastolic(Em and Am) parameters obtained from IVS, LV and RV free wall annulus:- Sm: systolic tissue annular velocity; Em: Early diastolic tissue annular velocity; Am: Late diastolic tissue annular velocity.

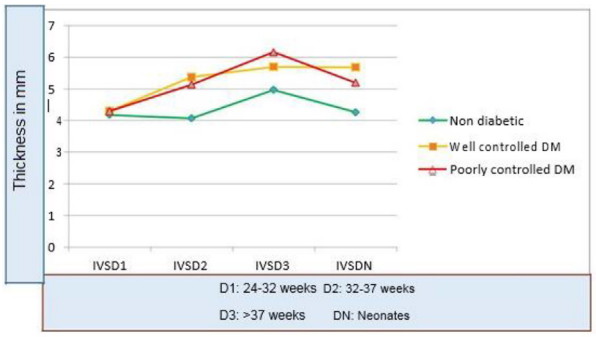

Fig. 2. Longitudinal changes in IVS thickness throughout pregnancy and in neonates in 3 groups.

respect to perinatal and neonatal morbidity indicators (Table 4). In our study, there were only 2 cases of perinatal asphyxia/acidosis. There were no perinatal deaths. Thus the prediction of perinatal mortality/asphyxia was not possible. As seen in Table 4 the proportion of fetuses showing intra partum CTG changes requiring delivery was similar among those with septal hypertrophy, 2 out of 26 (7.6%) as compared to those without septal hypertrophy, 16 out of 159 (10%) with the p value of 0.35. However, severe septal hypertrophy at term was strongly linked to neonatal problems like hypoglycaemia, hyperbilirubinemia and NICU stay >7 days. Persistent fetal shunts/small ASD and VSDs were commoner among foetuses with RV hypertrophy >90th centile (21% Vs 8.9% p 0.02). Septal/Myocardial hypertrophy was clearly associated with the increased risk of any one of the above mentioned neonatal problems. All together 20 neonates had NICU stay more than 7 days with the proportion of 3.93%, 10.25% and 27.27% among non-diabetics, well controlled and poorly controlled DM groups respectively. Prolonged NICU stay was predominantly attributed to neonatal hypoglycemia and RDS. Among the study participants there were 3 well controlled diabetic pregnant women who turned out to be poorly controlled at 37 weeks of gestation however these 3 infants did not show any perinatal/neonatal adverse outcome except for hyperbilirubinemia in one infant, whereas we did not find any crossover from poorly controlled to well controlled status on follow up in pregnancy. Therefore we have opted intension to treat analysis to compare structural and functional cardiac changes between three groups throughout the follow up.

None of the fetal cardiac functional parameters seemed to have association with adverse perinatal/neonatal outcome, except for RV TDI annular systolic velocity at term. Among 33 fetuses with RV tissue annular velocity <10th centile, 4 (12%) developed neonatal hypoglycaemia compared to 11 (7%) among 152 foetuses with RV tissue annular velocity > 10th centile, p-value being 0.04. Further assessment with Multivariate analysis showed that RV free wall thickness measured beyond 37 weeks of gestation [Exp(β) = 2.692, 95%CI: 1.091 and 6.643] and maternal glycemic control status [Well controlled Exp(β) = 8.727 95%CI: 1.496 and 50.908 and poorly controlled Exp(β) = 20.703, 95%CI: 3.007 and 142.524] were found to be the good independent predictors of neonatal hypoglycemia. However estimated fetal weight and IVS thickness did not fare well as independent predictors.

4. Discussion

Suboptimal maternal glycemic control is known to be associated with adverse perinatal/neonatal outcomes. Literature is sparse on the clinical utility of foetal echocardiography in diabetic pregnancies. There are few studies using TDI throughout pregnancy into the neonatal period, correlating with adverse perinatal outcome.

Similar to our results, Garg et al[4] noted significantly increased end-diastolic thickness at IVS, LV and RV among term foetuses of well controlled GDM mothers (FBS<100 mg/dl, PPBS<140 mg/dl). Balli et al[5] studied septal thickness among foetuses of diabetic mothers (mean HbA1C 5.79%) at 24, 28, 32 and 36 weeks and noted a significant increase in IVS thickness among them, specifically in later trimesters similar to our study. Thus, fetal IVS hypertrophy among diabetic pregnancies - is seen uniformly in the published literature.[6,7]

In our study, conventional 2D foetal Doppler parameters failed to demonstrate fetal myocardial dysfunction among diabetics. Balli et al[5] studied MV and TV E/A ratio among foetuses of diabetic

Table 4
Implications of foetal cardiac changes on perinatal and neonatal morbidity.

Adverse outcome	IVS thickness		LV thickness		RV thickness	
	<90th percentile (159)	>90th percentile (26)	<90th percentile (141)	>90th percentile (44)	<90th percentile (157)	>90th percentile (28)
CTG changes requiring delivery	16 (10%)	2 (7.6%)	14 (9.9%)	4 (9%)	15 (9.5%)	3 (10.7%)
P value	0.35		0.42		0.27	
Subtle cardiac abnormalities and persistent fetal shunts*	16 (10%)	4 (15.3%)	14 (9.9%)	6 (13.6%)	14 (8.9%)	6 (21.4%)
P value	0.598		0.301		0.02	
Hypoglycemia	7 (4.4%)	8 (30.7%)	6 (4.2%)	9 (20.4%)	8 (5.09%)	7 (25%)
P value	0.003		0.009		0.004	
Hyper Bilirubinemia	52 (32.7%)	13 (50%)	45 (31.9%)	20 (45.4%)	55 (35%)	10 (35.7%)
P value	0.40		0.06		0.277	
RDS	19 (11.9%)	2 (7.6%)	18 (12.7%)	3 (6.8%)	19 (12.1%)	2 (7.1%)
P value	0.610		0.344		0.601	
Prolonged NICU stay >7 days	13 (8.1%)	7 (26.9%)	11 (7.8%)	9 (20.4%)	12 (7.6%)	8 (28.5%)
P value	0.02		0.01		0.01	
Pooled adverse neonatal outcomes	57 (35.8%)	14 (53.8%)	48 (34%)	23 (52.2%)	57 (36.3%)	14 (50%)
P value	0.04		0.04		0.03	

IVS: inter ventricular septum, LV: Left ventricle, RV: Right ventricle, *: Cardiac abnormalities referred to persistent foramen ovale, persistent ductus arteriosus, tiny Atrial septal defects and tiny ventricular septal defects.

mothers (mean HbA1C 5.79%) and compared them to foetuses of non-diabetics at 24, 28, 32 and 36 weeks. They could not demonstrate any significant difference between the two groups, as in our study. In contrast, diastolic dysfunction, as reflected by lower E/A ratio, predominantly affecting RV, has been clearly demonstrated by other researchers.[4,6,7]

We could not demonstrate global myocardial dysfunction among foetuses of diabetic mothers at term, using the Modified-MPI. This is in contrast to earlier studies suggesting a higher MPI thus poorer global myocardial function among foetuses of diabetic women. Such myocardial dysfunction has been demonstrated among fetuses whether diabetes is mild,[8] or severe.[9]

Balli et al[5] performed TDI among foetuses of diabetic mothers at 24, 28, 32 and 36 weeks. They noted decreased annular systolic velocities across IVS and RV - from 28 weeks onwards but not across LV. Similarly, we noted reduced tissue annular systolic velocities across RV and IVS at term but not across LV. Foetuses with IVS and RV free wall thickness >90th centile showed poor annular systolic velocities at IVS an RV; thus, structural changes correlated well with systolic dysfunction at IVS and RV. Although diastolic dysfunction is expected among foetuses with myocardial hypertrophy, we could not demonstrate the same using TDI. In contrast, Pinar D et al demonstrated diastolic dysfunction in the RV using TDI among diabetic pregnancies compared to non-diabetic controls.[6]

Available literature describes cardiac changes in neonates of diabetic mothers compared to controls. However, longitudinal follow up throughout pregnancy into the neonatal period has been rarely reported.[10] We found that cardiac structural changes were persistent in the neonatal period, but functional changes were not apparent. Al-Biltagi et al[10] assessed cardiac functional changes using TDI among neonates of mothers with pre-gestational or GDM in comparison to neonates of non-diabetic mothers. They demonstrated no difference in tissue Doppler annular systolic and diastolic velocities among the three groups. Similarly, we could not demonstrate TDI changes between neonates of diabetic and non-diabetic mothers.

Performing a term fetal echo would be a useful exercise only if we could predict problems and improve neonatal outcome. Although foetal cardiac changes among diabetic women are well understood, their implications on the perinatal health are not well studied. Our results suggest that foetuses with significant myocardial hypertrophy are more likely to have problems in the neonatal period, such as hypoglycaemia, hyperbilirubinemia, prolonged NICU stays, and persistent foetal shunts. However, cardiac structural changes could not predict intrapartum foetal distress or perinatal asphyxia/death.

Bhorat et al[9] have observed adverse neonatal outcomes like perinatal mortality, poorer APGAR scores, acidosis, prolonged NICU admissions and neonatal cardiomyopathy more commonly among neonates with increased Tei index. They studied if Tei index can be used as a marker to predict adverse perinatal outcome among foetuses of poorly-controlled diabetic mothers (Mean sugar levels of 214.2 mg/dl, majority requiring insulin). They found that the Tei index greater than 0.52 has 100% sensitivity and 92% specificity in predicting adverse perinatal outcomes. The same group of authors further proved the utility of mod-MPI as an excellent predictor of above-mentioned adverse perinatal outcomes, even among women with mild glucose intolerance on diet.[8] However, in our study, cardiac changes could not predict intrapartum CTG changes or low APGAR. In our study, there were no perinatal mortality, and only 2 perinatal asphyxia/acidosis. Myocardial dysfunction was not apparent among neonates of diabetic women. None of our subjects had very high sugars despite labeled poorly controlled as per ADA criteria. Mean sugar values at term in the poorly controlled group in our study are FBS-96.44 ± 11.69 mg/dl and PPBS-131.67 ± 21.64 mg/dl. Mean RV Tei index in this poorly controlled group was 0.39, versus 0.37 in the non-diabetic controls. Thus our diabetic groups showed very subtle fetal TDI changes, and they could not probably predict the adverse perinatal outcome.

Although our study has not shown a correlation between fetal IVS hypertrophy and perinatal mortality, this negative correlation may not be extrapolated to a diabetic population with very high sugars, in whom IVS thickness may still be a simple predictive tool to detect perinatal fetal compromise. IVS thickness at term has proven to be useful in predicting stillbirth/neonatal distress/mortality/neonatal cardiac failure in a group of poorly controlled pre-gestational diabetic women.[11]

According to our results, perfect glycemic control is beneficial as, even borderline high sugars lead to fetal IVS hypertrophy and these foetuses are at risk of neonatal hypoglycaemia, hyperbilirubinemia, persistent foetal shunts (altered transitional circulation), prolonged NICU stay all contribute to significant neonatal morbidity in these neonates. Especially, neonatal hypoglycaemia is an important preventable cause of long term neurological morbidity which can be predicted using IVS thickness. This correlation has not been well studied. Anticipation, prevention, early detection and appropriate

correction of hypoglycaemia would be beneficial. A Katheria et al demonstrated that GDM infants often exhibit altered systemic flow, delayed newborn hemodynamic circulatory transition or combination of both resulting in higher incidence of persistent foramen ovale, patent ductus arteriosus for prolonged period after birth.[12]

There is an association between fetal IVS hypertrophy at term and maternal glycemic control. Fetal IVS thickness is easily measurable at term. We propose this is a useful additional tool at term pregnancy to increase surveillance on these neonates, thus reducing neonatal complications. We could demonstrate fetal myocardial dysfunction only at term using TDI. Cardiac functional changes no longer persisted in the neonates of diabetic women. Cardiac functional changes could not predict perinatal/neonatal complications. Performing mod-MPI and TDI needs expertise, high-end ultrasound machine, and consumes time. In a group of fairly controlled pregnant diabetics, the clinical usefulness of performing these functional parameters seems limited.

4.1. Limitations

Women in the “poorly controlled” group did not have very high sugars; their sugar values were only 10–30 mg/dl higher than the ADA criteria. Therefore, our results, especially on functional abnormalities of the heart, cannot be generalized to women with very poor glycemic control. We did not have a large group of pre-gestational diabetes; therefore, we could not assess the impact of pre-gestational diabetes as well.

5. Conclusion

Our study shows a significant association between fetal myocardial hypertrophy and maternal glycemic control among GDM pregnancies. There also seems to be an association between fetal myocardial hypertrophy and some of the adverse perinatal events including neonatal hypoglycemia. However these newborns were not found to have clinically relevant cardiac comorbidities even though there was significant septal hypertrophy in utero.

Conflicts of interest

None.

References

1. Atlas D. *International Diabetes Federation. IDF Diabetes Atlas*. 7th ed. Brussels, Belgium: International Diabetes Federation; 2015.
2. Mithal A, Bansal B, Kalra S. Gestational diabetes in India: science and society. *Indian journal of endocrinology and metabolism*. 2015 Nov;19(6):701.
3. Farrar D, Simmonds M, Bryant M, et al. Hyperglycaemia and risk of adverse perinatal outcomes: systematic review and meta-analysis. *bmj*. 2016 Sep 13;354:i4694.
4. Garg S, Sharma P, Sharma D, Behera V, Durairaj M, Dhall A. Use of fetal echocardiography for characterization of fetal cardiac structure in women with normal pregnancies and gestational diabetes mellitus. *J Ultrasound Med*. 2014 Aug;33(8):1365–1369.
5. Balli S, Pac FA, Ece İ, Oflaz MB, Kibar AE, Kandemir Ö. Assessment of cardiac functions in fetuses of gestational diabetic mothers. *Pediatr Cardiol*. 2014 Jan 1;35(1):30–37.
6. Dervisoglu Pinar, Kosecik Mustafa, Kumbasar Serkan. Effects of gestational and pregestational diabetes mellitus on the foetal heart: a cross-sectional study. *J Obstet Gynaecol*. 2018. https://doi.org/10.1080/01443615.2017.1410536.
7. Babovic Ivana, Arandjelovic Milica, Plesinac Snezana, Kontic-Vucinic Olivera, Radunovic Nebojsa. Maternal glycoregulation in pregnancies complicated by diabetes mellitus in the prediction of fetal echography findings and perinatal outcomes. *J Obstet Gynaecol Res*. March 2018;44(No. 3):432–439. https://doi.org/10.1111/jog.13537.
8. Bhorat Ismail, Pillay Morgan, Reddy Tarylee. Determination of the Fetal Myocardial Performance Index in women with Gestational Impaired Glucose Tolerance and to assess whether this parameter is a possible prognostic indicator of adverse fetal outcome. *J Matern Fetal Neonatal Med*. 2017. https://doi.org/10.1080/14767058.2017.1334047.
9. Bhorat IE, Bagratee JS, Pillay M, Reddy T. Use of the myocardial performance index as a prognostic indicator of adverse fetal outcome in poorly controlled gestational diabetic pregnancies. *Prenat Diagn*. 2014 Dec 1;34(13):1301–1306.
10. Al-Biltagi M, Tolba OA, Rowisha MA, Mahfouz AE, Elewa MA. Speckle tracking and myocardial tissue imaging in infant of diabetic mother with gestational and pregestational diabetes. *Pediatr Cardiol*. 2015 Feb 1;36(2):445–453.
11. Elmekkawi SF, Mansour GM, Elsafty MS, Hassanin AS, Laban M, Elsayed HM. Prediction of fetal hypertrophic cardiomyopathy in diabetic pregnancies compared with postnatal outcome. *Clin Med Insights Women's Health*. 2015;8:39–43. https://doi.org/10.4137/CMWH.S32825.
12. Katheria A, Leone T. Altered transitional circulation in infants of diabetic mothers with strict antenatal obstetric management: a functional echocardiography study. *J Perinatol*. 2012;32:508–513. https://doi.org/10.1038/jp.2011.135.