DOI: 10.7860/JCDR/2016/17993.8079

Original Article

Obstetrics and Gynaecology Section

Fetal Cardiodynamics by Echocardiography in Insulin Dependent Maternal Diabetes and Its Correlation with Pregnancy Outcome

RASHMI PILANIA[1], POOJA SIKKA[2], MANOJ K. ROHIT[3], VANITA SURI[4], PRAVEEN KUMAR[5]

ABSTRACT

Introduction: Maternal diabetes mellitus is associated with an increased risk of fetal and neonatal morbidity and mortality. Usual screening tests have not proved to be good prognostic indicators of fetal distress. Fetal cardiodynamics is potentially a useful screening tool.

Aim: To determine if cardiodynamics of the fetus differ in pregnancy with diabetes requiring insulin than those without and to determine whether cardiodynamics predict fetal and neonatal outcomes.

Materials and Methods: This prospective case control study was carried out in 40 pregnant women with diabetes who required insulin for blood sugar control. Twenty uncomplicated pregnant women were taken as controls. Systolic and diastolic cardiac functions along with interventricular septal thickness were assessed at 26-28 weeks and again at 34-36 weeks of gestation in fetuses by echocardiography. Fetal and neonatal adverse outcomes were evaluated in terms of major and minor morbidity.

Results: Among all parameters, E/A ratio across both mitral and tricuspid valves, myocardial performance index and cardiac output were significantly different in fetuses of diabetic mothers at both gestations. However, pulmonary vein pulsatility index and interventricular septal thickness were similar between the two groups. At 26-28 weeks of gestation myocardial performance index correlated with abnormal biophysical profile whereas cardiac output correlated with minor morbidity. At 34-36 weeks of gestation, cardiac output correlated with abnormal biophysical profile while both MPI and cardiac output correlated with minor morbidity.

Conclusion: Echocardiographic parameters of fetuses of diabetic women significantly differed from those of uncomplicated non-diabetic women. However, only myocardial performance index and cardiac output correlated with adverse fetal and neonatal outcomes.

Keywords: Cardiac output, Diabetes mellitus, Echocardiography, Myocardial performance index

INTRODUCTION

Maternal diabetes mellitus is associated with an increased risk of fetal morbidity, still births and neonatal morbidity and mortality. Improvements in fetal surveillance and perinatal management have led to reduction in diabetes related complications. Despite this, the incidence of complications is higher than in the general population. An important marker of fetal compromise is intrauterine growth restriction, which may not be found in diabetic pregnancies. Various non-invasive monitoring techniques including fetal biophysical profile, nonstress test, peripheral Doppler have not proved to be good prognostic indicators of fetal distress and unexplained fetal deaths still occur in diabetic pregnancies [1-4].

Fetal echocardiography is often carried out in diabetic mothers because of increased risk of structural cardiovascular malformations in their fetuses. The diagnostic yield however is low [5]. Structural cardiovascular malformations are uncommon, however, changes in cardiovascular flow patterns in fetuses of diabetic mothers may have prognostic significance. Studies have demonstrated impaired development of cardiac and venous flow patterns in fetuses of diabetic mothers as early as 12 weeks of gestation [6]. These include altered fetal cardiac diastolic function, increased blood flow in the fetal aorta and pulmonary vasculature and higher peak velocities at the level of aortic and pulmonary outflow tracts [6,7]. Significantly increased Pulmonary Vein Pulsatility Index (PVPI) and increased left and right ventricle Myocardial Performance Index (MPI) is also noted [8,9]. Thus, fetal cardiodynamics may potentially predict future fetal compromise.

AIM

This study was done with the aim to study the cardiodynamics of fetuses of diabetic pregnant women requiring insulin by echocardiography at two different gestations and then to correlate cardiodynamics at these two periods with the pregnancy outcomes.

MATERIALS AND METHODS

This study was performed in 40 pregnant women with pre-existing diabetes mellitus or Gestational Diabetes Mellitus (GDM) requiring insulin and 20 non-diabetic pregnant women in the Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh. The study period was from January 2012 to June 2013. The research protocol was approved by the institute ethics committee and was in accordance with the Helsinki Declaration of 1975 that was revised in 2000. Written informed consent was obtained from all subjects.

Pregnant women with type 1 or type 2 diabetes mellitus on insulin or patients with Gestational Diabetes Mellitus (GDM) diagnosed by glucose tolerance test using 75g glucose before 26 weeks of gestation and requiring insulin were included in the study. Twenty non-diabetic healthy women with no high risk factors were taken as controls after a normal glucose tolerance test with 75g glucose, following WHO criteria.

Patients with GDM on diet therapy alone, presence of any fetal congenital malformation, fetuses with intrauterine growth restriction at the time of recruitment and patients with gestational hypertension or preeclampsia at the time of recruitment were excluded from the study.

Fetal echocardiography was performed by a single paediatric cardiologist in all participant women to study the circulatory haemodynamics at 26-28 weeks of gestation which was repeated at 34-36 weeks of gestation. Both the systolic and diastolic functions were assessed and the following parameters were noted:

E/A ratio

Pulsed wave velocity waveforms were obtained across both tricuspid and mitral valve. Doppler of entry flow of left and right ventricle was obtained at the cooptation of mitral and tricuspid valves respectively, in the apical four chamber view. Peak E and A wave velocities were recorded in meters/second and E/A ratio calculated.

Cardiac Output

Aortic arterial Doppler waveforms was obtained from the aorta in the long axis of the 5-chamber view of the heart. The peak or the maximum velocity was obtained by measuring the highest velocity of the time velocity Doppler signal. The time-to-peak velocity was measured from the beginning of the waveform to the point of peak velocity.

Left sided cardiac output (ml/min) $=3.14*(Ao/2)^2*VTI*HR$

Ao = aortic valve diameter; VTI=Velocity Time Integral; HR=Heart Rate.

Blood Flow Velocity Waveforms through Pulmonary Vein

The flow analysis through pulmonary vein was performed using the pulsed Doppler and color flow mapping. PVPI was obtained during the periods of fetal apnea by placing pulsed Doppler sample volume over the right superior pulmonary vein, as near as possible to the junction with left atrium and was calculated by subtracting presystolic velocity from systolic velocity and dividing the result by mean velocity.

PVPI = systolic velocity-presystolic velocity/mean velocity

Thickness of Interventricular Septum

The thickness of interventricular septum was measured under suspended maternal voluntary respiration without fetal breathing movement or fetal body movement in the transverse four chambered view with the cursor perpendicular to interventricular septum at the end diastolic phase.

Myocardial Performance Index

The MPI was calculated as: (IRT+ICT)/ET

IRT= Isovolumic Relaxation Time; ICT= Isovolumic Contraction Time; ET= Ejection Time.

Three values of each parameter were taken. Average of the 3 assessments was considered.

In both cases and controls, HbA1c was sent at the time of both the measurements. Biophysical profile of the fetus, peripheral Doppler and blood sugar monitoring was performed in diabetic mothers as per maternal and fetal indications. All neonates were followed up from birth till discharge from hospital.

Correlation at the end of study was performed between these five echocardiographic parameters and fetal and neonatal adverse outcomes. Fetal and neonatal adverse outcome was evaluated in terms of major and minor morbidity. Major morbidity was defined as abnormal biophysical profile (BPP) defined as BPP< 8/10 or S/D across umbilical artery>3; preterm birth before 37 completed weeks; fetal distress defined as persistent fetal bradycardia <110/minute or meconium stained liquor; intrauterine death of fetus; hypoxic ischemic encephalopathy; cardiac failure; respiratory distress syndrome or fetal academia. Minor morbidity was defined as presence of birth weight>4 kg, low apgar<7at 1 and 5minutes, hypoglycaemia, polycythemiaor hypotension.

STATISTICAL ANALYSIS

The statistical analysis was carried out using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows). Mean and medians was calculated for all quantitative variables and the measures of dispersion (standard deviation and standard error) were calculated. Normality of data was checked by measures of Kolmogorov Smirnov tests of normality. For normally distributed data, means were compared by using t-test. For skewed data and scores, Mann–Whitney test was applied. Qualitative or categorical variables were described as frequencies and proportions. Proportions were compared by using Chi-square or Fisher's-exact test whichever was applicable. All statistical tests were two-sided. Statistical significance was reached at $p< 0.05$.

RESULTS

Both groups were similar with regard to maternal age (28.7±3.5 years in diabetic group and 27.4±3.2 years in control group, p=0.130). Body mass index of the diabetic group was higher compared to the control group (25.02±2.46 kg/m^2 of diabetic group and of the non-diabetic group was 23.6±1.69 kg/m^2, p=0.026). In the diabetic group 18 women had GDM while the remaining 22 had type 2 diabetes mellitus. Stringent blood glucose monitoring and fetal monitoring by regular biophysical profile and biometry was carried out in all patients. The mean HbA1C of GDM women at 26-28 weeks of gestation was 6.7±1.31% and at 34-36weeks of gestation was 6.1±1.01%. This was comparable to type 2 diabetic pregnant women whose HbA1Cat similar gestations were 6.6±1.53% and 6.2±0.91% respectively. p=0.849(26-28 weeks), p=0.926(34-36weeks). Women in the diabetic group delivered earlier at mean gestational age of 37.28±1.59 weeks while women in control group delivered at the mean gestational age of 38.5±1.42 weeks (p=0.005). The mean birth weight of fetuses in study group were similar (2.9±0.55 kg and in control group was 2.6±0.388 kg, p=0.077).

Among the 40 diabetic group patients, 22.5% had abnormal BPP and none among the control group had an abnormal BPP (p=0.046). Only 1 woman among the diabetic group had an intrauterine fetal death and none among the control group had intrauterine fetal death. Among 39 neonates in diabetic group, 28.2% had polycythemia whereas none among the neonates in the control group had polycythemia (p=0.016). Among 39 neonates in diabetic group 33.3% had hypoglycaemia, whereas none among the neonates in control group had hypoglycaemia (p=0.002). None of the neonates in either group developed acidemia, respiratory distress syndrome, hepatic ischemic encephalopathy or cardiac failure.

Fetal cardiodynamic parameters at 26-28 weeks and 34-36 weeks of gestation are given in [Table/Fig-1,2] respectively. Among all the parameters E/A ratio across both mitral and tricuspid valve, Myocardial Performance Index (MPI) and cardiac output were significantly different in fetuses of diabetic mothers at both gestations. However, PVPland interventricular septal thickness was similar between the two groups at both gestations.

Of the 40 diabetic women, 9 had abnormal BPP. Among all these parameters tested, only MPI at 26-28 weeks of gestation correlated with abnormal BPP (p=0.008). ROC analysis was used to assess how efficiently the MPI at 26-28 weeks of gestation predicted the chances of abnormal BPP. Area under the curve was 0.857. Value of MPI of 0.595 at 26-28 weeks of gestation generated sensitivity of 88.9% and specificity of 72.5%.

Cardiac output at 26-28 weeks of gestation had significant correlation with minor morbidity comprising of birth weight >4kg, low apgar at 1 and 5 minutes, polycythemia, hypoglycaemia or hypotension (p=0.015) [Table/Fig-3a]. Using ROC analysis, area under the curve was 0.669, the value of cardiac output of 173.05 ml/min at 26-28

weeks of gestation generated sensitivity of 71.4 % and specificity 56% for the prediction of composite minor outcomes.

Out of 40 diabetic women, 4 women delivered prior to echo-cardiography at 34-36 weeks of gestation. These 4 women were excluded from the 34-36 weeks analysis. Of the remaining 36 women, 8 had abnormal BPP. Only cardiac output at 34-36 weeks correlated with abnormal BPP (p=0.013). Area under the ROC curve was 0.795. All other parameters did not correlate with any major adverse outcome [Table/Fig-3b]. The value of cardiac output of 312.9 ml/min generated sensitivity of 87.5% and specificity of 64% in predicting an abnormal BPP. At 34-36 weeks of gestation both cardiac output and MPI had significant correlation with minor morbidity. Using ROC analysis, with area under the curve of 0.705, the value of cardiac output of 328.450 ml/minute at 34-36 weeks of gestation generated sensitivity of 66 % and specificity of 70% and the value of MPI of 0.61 with area under the curve of 0.729 generated sensitivity of 71 % and specificity of 56% in predicting minor morbidity.

	Diabetic group N=40	Controls N=20	p value
Mean E/A across mitral valve	0.69± 0.06	0.75±0.04	<0.001
Mean E/A across tricuspid valve	0.70±0.09	0.76±0.06	0.016
Mean Cardiac output (ml/min)	192.9±67.74	130.9±20.3	<0.001
Mean myocardial performance index	0.583±0.06	0.493±0.06	0.000
Mean pulmonary vein pulsatility index	0.548 ±0.23	0.514±0.153	0.556
Mean interventricular septal thickness (cm)	0.406±0.135	0.345±0.057	0.059

[Table/Fig-1]: Fetal echocardiographic parameters at 26-28 weeks of gestation.

	Diabetic group N=36	Controls N=20	p-value
Mean E/A across mitral valve	0.75±0.062	0.78±0.056	0.046
Mean E/AMean E/A across tricuspid valve	0.73±0.074	0.79±0.086	0.013
Mean Cardiac output (ml/min)	316.057± 92.82	251.188±75.88	0.010
Mean myocardial performance index	0.62±0.07	0.58±0.07	0.047
Mean pulmonary vein pulsatility index	0.71± 0.229	0.60±0.279	0.144
Mean interventricular septal thickness (cm)	0.56±0.47	0.398±0.0827	0.118

[Table/Fig-2]: Fetal cardiodynamics parameters at 34-36 weeks of gestation.

	Abnormal BPP N=9	Normal BPP N=31	p-value
E/A Mitral valve	0.69±0.09	0.69± 0.06	0.974
E/A Tricuspid valve	0.71±0.03	0.71± 0.13	0.828
Interventricular septal thickness	0.37± 0.07	0.41± 0.14	0.483
Mean myocardial performance index	0.63±0 .04	0.57± 0.06	0.008
Cardiac output	195.52± 087.93	192.14± 62.46	0.897
Mean pulmonary vein pulsatility index	0.47± 0.25	0.57± 0.22	0.232

[Table/Fig-3a]: Biophysical profile at 26-28 weeks of gestation- correlation with cardiodynamics.

	Abnormal BPP N=8	Normal BPP N=28	p-value
E/A Mitral valve	0.74±0.08	0.76± 0.06	0.432
E/A Tricuspid valve	0.77±0.08	0.70±0.08	0.237
Interventricular septal thickness	0.46±0.09	0.61± 0.54	0.461
Mean myocardial performance index	0.63±0.04	0.57± 0.06	0.659
Cardiac output	385.9± 60.9	297.7± 92.70	0.013
Mean pulmonary vein pulsatility index	0.67±0.20	0.72± 0.24	0.591

[Table/Fig-3b]: Biophysical profile at 34-36 weeks of gestation- correlation with cardiodynamics.

DISCUSSION

Maternal diabetes mellitus is a common medical disorder that can significantly affect the fetal heart in both structure and function. Most cardiodynamic parameters differed between diabetic mothers and controls at both 26-28 and 34-36 weeks of gestation. However, unlike earlier studies, PVPI that reflects fetal diastolic function and interventricular septal thickness were similar between the two groups at both gestations [8,10,11]. Fetal interventricular septal thickness reflects ventricular mass and correlates with HbA1C levels [12]. It was probably not increased in this study because the diabetes was well controlled in our patients. Impaired diastolic function has been consistently found in previous studies [13,14]. In this study also, reduced E/A ratio across both mitral and tricuspid valves was found in diabetics suggesting increased ventricular stiffness at both gestations. Altered metabolic environment and fluctuations in maternal blood sugar levels may be responsible for the impaired diastolic function. Similarly cardiac output, both absolute and per kilogram of estimated fetal weight was increased in fetuses of diabetic mothers. This has previously been reported even in patients with well-controlled type-I diabetes mellitus [9]. Increased cardiac output was seen despite impaired myocardial performance. This suggests that cardiac output is increased due to increased fetal metabolic demand and altered circulatory dynamics. MPI is a complex parameter capable of estimating combined systolic and diastolic performance and is independent of heart rate and loading conditions. Higher index values correspond to more pathological states with overall cardiac dysfunction. In this study also, mean MPI at both gestations was increased in diabetics reflecting impaired myocardial performanceeven in well controlled diabetic patients [14].

There were only few adverse fetal and neonatal outcomes due to close monitoring, early hospitalization, strict blood sugar control, timely betamethasone therapy and termination of pregnancy at 37-38 weeks of gestation. None of the women in the diabetic group went post-dates. Among the 40 diabetic pregnant women, 22.5% had abnormal BPP while none of the control group had an abnormal BPP. This confirms that despite adequate blood sugar control, fetuses were still at risk of asphyxia or academia.

Despite several parameters of fetal cardiodynamics differing in fetuses of cases and controls, only a few of these parameters correlated with adverse fetal outcomes. At 26-28 weeks of gestation, among all these parameters, only MPI correlated with abnormal BPP. ROC analysis generated sensitivity of 88.9% and specificity of 72.5% suggesting that this parameter measured as early as 26-28 weeks of gestation could predict adverse fetal outcomes much later in pregnancy. At 34-36 weeks however MPI was no longer a good predictor of adverse fetal outcomes since it correlated only with minor morbidity and not with major adverse outcomes. At 34-36 weeks gestation cardiac output was a much predictor of adverse fetal outcomes. This suggests that that increasing cardiac output in later pregnancy in diabetics correlates better with adverse outcomes as compared to the second trimester. Conversely, MPI that reflects global cardiac function is a better predictor of adverse fetal outcomes in the second trimester.

LIMITATION

There are some limitations of this study. Comparison of fetal cardiodynamic parameters between patients with GDM and preexisting type 2 diabetes mellitus was not carried out since only

a small number of adverse fetal and neonatal events were seen. Intra-operator variability in echocardiographic parameters was also not measured in this study.

Cardiodynamic parameters are a simple and non-invasive tool to predict adverse fetal outcomes in diabetic mothers as early as the second trimester of pregnancy. Large prospective trials should be carried out to see if monitoring these parameters also predict hard clinical end points like intra-uterine fetal deaths and improve fetal outcomes when added to currently available tests like fetal biophysical profile and nonstress test.

CONCLUSION

Echocardiographic parameters of fetuses of diabetic women were significantly different from those of uncomplicated non-diabetic women even though diabetic status was well controlled. However, only MPI at 26-28 weeks and cardiac output at 34-36 weeks of gestation correlated with adverse fetal and neonatal outcomes.

REFERENCES

[1] Salvesen DR, Higueras MT, Mansur CA, Freeman J, Brudenell JM, Nicolaides KH. Placental and fetal Doppler velocimetry in pregnancies complicated by maternal diabetes mellitus. *Am J Obstet Gynecol*. 1993;168:645-52.

[2] Salvesen DR, Higueras MT, Brudenell JM, Drury PL, Nicolaides KH. Doppler velocimetry and fetal heart rate studies in nephropathic diabetics. *Am J Obstet Gynecol*. 1992;67:1297-303.

[3] Ishimatsu J, Matsuzaki T, Yakushiji M, Hamada T. Blood flow velocity waveforms of the fetal middle cerebral artery in pregnancies complicated by diabetes mellitus. *Kurume Med J*. 1995;42:161-66.

[4] Reece EA, Hagay Z, Moroder W, DeGennaro N, Homko C, Wiznitzer A. Is there a correlation between aortic Doppler velocimetric findings in diabetic pregnant women and fetal outcome? *J Ultrasound Med*. 1996;15:437-40.

[5] Sekhavat S, Kishore N, Levine JC. Screening fetal echocardiography in diabetic mothers with normal findings on detailed anatomic survey. *Ultrasound Obstet Gynecol*. 2010;35:178-82.

[6] Rizzo G, Arduini D, Capponi A, Romanini C. Cardiac and venous blood flow in fetuses of insulin-dependent diabetic mothers: evidence of abnormal haemodynamics in early gestation. *Am J Obstet Gynecol*. 1995;173:1775-81.

[7] Rizzo G, Arduini D, Romanini C. Cardiac function in fetuses of type I diabetic mothers. *Am J Obstet Gynecol*. 1991;164:837-43.

[8] Zielinsky P, Piccoli AL, Teixeira L, et al. Pulmonary vein pulsatility in fetuses of diabetic mothers: prenatal Doppler echocardiographic study. *Arq Bras Cardiol*. 2003;81:604-07.

[9] Lisowski LA, Verheijen PM, De Smedt MM, Visser GH, Meijboom EJ. Altered fetal circulation in type-1 diabetic pregnancies. *Ultrasound Obstet Gynecol*. 2003;21:365-69.

[10] Tsyvian P, Malkin K, Artemieva O, Wladimiroff JW. Assessment of left ventricular filling in normally grown fetuses, growth-restricted fetuses and fetuses of diabetic mothers. *Ultrasound ObstetGynecol*. 1998;12:33-38.

[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 Womens Health*. 2015;8:39-43.

[12] El-Ganzoury MM, El-Masry SA, El-Farrash RA, Anwar M, AbdEllatife RZ. Infants of diabetic mothers: echocardiographic measurements and cord blood IGF-I and IGFBP-1. *Pediatr Diabetes*. 2012;13:189-96.

[13] Hatém MA, Zielinsky P, Hatém DM, et al. Assessment of diastolic ventricular function in fetuses of diabetic mothers using tissue Doppler. *Cardiol Young*. 2008;18:297-302.

[14] Tsutsumi T, Ishii M, Eto G, Hota M, Kato H. Serial evaluation for myocardial performance in fetuses and neonates using a new Doppler index. *Pediatr Int*. 1999;41:722–27.

PARTICULARS OF CONTRIBUTORS:

1. Senior resident, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, India. (Was Junior Resident, Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh at time of research).
2. Associate Professor, Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
3. Professor, Department of Cardiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
4. Professor, Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
5. Professor, Department of Paediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Pooja Sikka,
Associate Professor, Department of Obstetrics and Gynaecology, Postgraduate Institute of Medical Education and Research,
Sector 12, Chandigarh- 160012, India.
E-mail: drpoojasikka@yahoo.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Nov 25, 2015**
Date of Peer Review: **Jan 09, 2016**
Date of Acceptance: **May 07, 2016**
Date of Publishing: **Jul 01, 2016**