Use of the myocardial performance index as a prognostic indicator of adverse fetal outcome in poorly controlled gestational diabetic pregnancies.

ORIGINAL ARTICLE

Use of the myocardial performance index as a prognostic indicator of adverse fetal outcome in poorly controlled gestational diabetic pregnancies

Ismail E. Bhorat[1]*, Jayanthilall S. Bagratee[1], Morgan Pillay[1] and Tarylee Reddy[2]

[1]Department of Obstetrics and Gynaecology, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa
[2]Biostatistics Unit, Medical Research Council, Durban, South Africa
*Correspondence to: Ismail E. Bhorat. E-mail: bhorat@worldonline.co.za

ABSTRACT

Objective The aim of this study was to determine whether there are any changes in cardiac function in fetuses of poorly controlled gestational diabetics and whether these changes influence perinatal outcome.

Methods Twenty-nine pregnant women with severe gestational diabetes on insulin therapy in the third trimester of pregnancy were recruited and matched with 29 women with normal pregnancies (control group). Using Doppler echocardiography, the modified myocardial performance index (Mod-MPI) and E wave/A wave peak velocities (E/A) ratios were determined. Placental resistance Doppler markers were also determined in both groups. Adverse perinatal outcome was defined as perinatal death, admission to the neonatal intensive care unit, cord pH <7.15, 5-min Apgar score <7 and presence of cardiomyopathy.

Results The median Mod-MPI was increased (0.59 vs 0.38; $p < 0.0001$) and the E/A ratio was decreased (0.65 vs 0.76; $p < 0.0001$) in fetuses of diabetic mothers compared with controls. An MPI >0.52 had a sensitivity of 100% [95% confidence interval (CI) 85–100%] and specificity of 92% (95% CI 70–92%) for prediction of adverse perinatal outcome, including one stillbirth and one neonatal death. No abnormal outcomes occurred in the control group.

Conclusions There is significant impairment of cardiac function in fetuses of poorly controlled gestational diabetics. Mod-MPI and E/A ratio have the potential to improve fetal surveillance in diabetic pregnancies. © 2014 John Wiley & Sons, Ltd.

Funding sources: None
Conflicts of interest: None declared

INTRODUCTION

Fetal echocardiography has been used for non-invasive evaluation of human fetal cardiac anatomy, function and haemodynamics.[1–3] A Doppler index of combined systolic and diastolic ventricular myocardial performance, the Tei index or myocardial performance index (MPI) has been proposed as a potential useful predictor of global cardiac function, which is not influenced by ventricular geometry and heart rate.[1] MPI or the Tei index is defined as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET).[1–3] The equation of the MPI is thus (ICT + IRT)/ET. To improve reproducibility, the technique of acquisition in the fetus has evolved to a modified MPI (Mod-MPI).[4–6]

The E wave/A wave peak velocity (E/A) ratio at the mitral valve (MV) is also used as an indicator of ventricular diastolic function.

Fetal complications in gestational or pregestational diabetes without microvascular complications are not related to placental insufficiency but rather fetal hyperinsulinism.[7] The best prenatal screening method of pregnancies in diabetic mothers remains elusive. Umbilical artery (UA) Doppler velocimetry is widely used to monitor high-risk pregnancies; however, it has not been shown to be an effective test of fetal well-being in diabetic pregnancies.[8] Similarly, the efficacy of ductus venosus Doppler velocimetry for monitoring fetuses of diabetic pregnancies is unsatisfactory.[9]

Impaired cardiac function in fetuses of diabetic pregnancies in the second and third trimesters is well documented.[10,11] Increased MPI, suggesting impairment of global myocardial performance, has been reported in small numbers of fetuses of diabetic mothers in mid to late gestation.[12,13] Figueroa *et al.*[14] also demonstrated a modest increase in Mod-MPI values in fetuses of diabetic mothers, but Mod-MPI did not predict newborns with complications.

This aim of this study was to investigate the cardiac function using the Mod-MPI and E/A ratios in fetuses of poorly controlled gestational diabetics to determine whether these parameters predicted perinatal outcome.

METHODS

This was a prospective cross-sectional study of the Mod-MPI and E/A ratios in fetuses of diabetic pregnancies conducted at the tertiary referral Fetal Unit at Inkosi Albert Luthuli Central Hospital in Durban, South Africa. Severe or poorly controlled diabetics are generally referred to our unit for further management. Between November 2012 and July 2013, 29 women with gestational diabetes on insulin therapy in the third trimester were recruited and matched (for gestational age and maternal age at inclusion) with 29 women with normal pregnancies, which served as the control group All patients in the study group were suboptimally to poorly controlled diabetics. Exclusion criteria were multiple pregnancies, congenital malformations, evidence of placental-mediated disease and abnormal fetal heart rates (either tachycardia or bradycardia). Placental-mediated disease was defined by either the presence of growth restriction (AC <10th percentile for gestational age with an elevated UA resistance index (RI) >90th percentile for gestational age) and/or presence of preeclampsia.

Using Doppler echocardiography, the Mod-MPI and E/A ratios were determined (refer to the succeeding discussions).

Fetal echocardiography using either an E8 General Electric Voluson ultrasound system (GE Medical Systems, WI, USA) or Siemens Antares ultrasound system (Siemens Medical Systems, Malvern PA, USA) was performed in each woman. The four chamber view, outflow tract views, triple vessel view, longitudinal view of the aortic arch and colour flow mapping were used to screen for cardiac malformations.

The Mod-MPI was calculated in the fetal left ventricle as originally described by Hernandez-Andrade *et al.*[6] (Figure 1). A cross-sectional image of the fetal thorax at the level of the four chamber view with an apical projection of the heart was obtained. The Doppler sample was opened to 3 mm and placed in the internal leaflet of the MV. In this location owing to its closeness to the aortic valve (AV), the opening and closing AV clicks were registered. The angle of insonation was always <30°. E/A waveform was always displayed as positive flow. The Doppler gain was lowered as far as possible to clearly visualize the echoes corresponding to the opening and closing clicks of the two valves at the beginning and at the end of the MV and aortic waveforms. The Doppler sweep velocity was set at 5 cm/s and wall motion filter at 300 Hz. The three periods were estimated as follows: ICT from beginning of MV closure to AV opening, ET from AV opening to closure and IRT from AV closure to MV opening. The Mod-MPI = (ICT + IRT)/ET. We have previously documented high levels of interobserver and intraobserver variability agreement (I. B. and J. B. as the operators) for the MPI and its components in our article establishing reference intervals of Mod-MPI in normal pregnancies.[15]

The E wave (early ventricular filling) and A wave (active atrial filling) peak velocities and the ratio between them (E/A ratio) at the level of the MV as an index of ventricular diastolic function were calculated. In addition to the echocardiography data, sonographic data including estimated fetal weights and amniotic fluid indices were determined and recorded. The

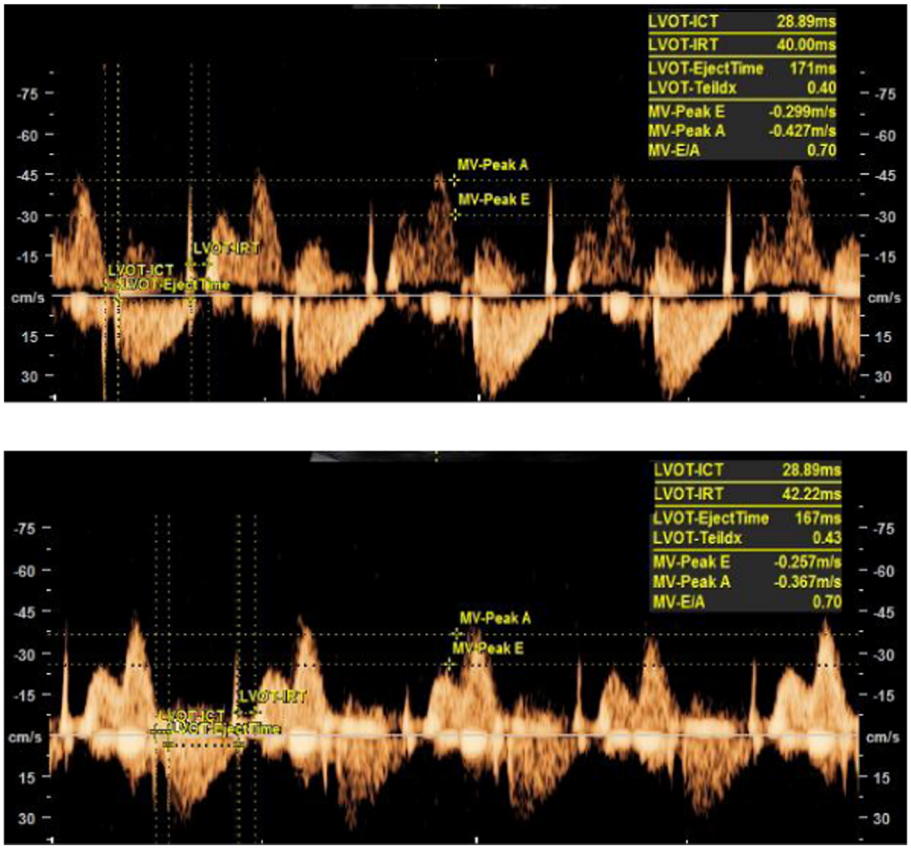

Figure 1 Normal myocardial performance index and E wave/A wave peak velocity ratio Doppler tracings at the mitral valve

UA RI, middle cerebral artery RI and ductus venosus pulsatility index (PI) were also determined in both groups.

Patients were delivered according to existing standard protocols for diabetic pregnant patients at our institution, which includes nonreassuring fetal cardiotocography (CTG) findings, poor biophysical profiles or persistent elevations of UA RI. If fetal monitoring was satisfactory, delivery was delayed until 39–40 weeks after which the patient would be induced or caesarean section performed for obstetrical reasons.

Pregnancy outcomes were recorded in both groups. An abnormal outcome was defined as any of the following: stillbirth, neonatal death, neonatal intensive care unit admissions, tachypnea with pulmonary oedema, neonatal cord pH <7.15, 5-min Apgar score <7 and cardiomyopathy, which is defined in this article as hypertrophic cardiomyopathy characterized by marked thickening of the interventricular septum and ventricular walls resulting in systolic and diastolic dysfunction (infants of diabetic mothers are known to be at increased risk for this type of cardiomyopathy). Cardiac Doppler data were not used by clinicians in the management of the diabetic patients.

STATISTICAL METHODS

Data were collected in MS Excel 2004 (Microsoft, Redwoods, WA, USA) and analyses were performed using STATA/SE version 12.0 (Stata Corp, College Station, TX, USA). Unpaired *t*-tests and the Wilcoxon rank sum test were used to compare continuous variables between two groups.

RESULTS

Twenty-nine pregnant women with severe gestational diabetes mellitus on insulin therapy (study group) were matched with 29 controls. The 29 patients in the study group were all suboptimally to poorly controlled diabetics requiring insulin therapy. The mean blood glucose level on assessment at the unit was 11.9 mmol/L (range between 8.3 mmol/L and 15.9 mmol/L). The majority of these patients required admission to stabilize the blood glucose levels with additional insulin therapy. This would explain the high fetal adverse outcome in the diabetic group (58%). Mode of delivery was caesarean section in 72% of patients in the study group for a combination of factors including fetal distress and macrosomia, with vaginal births in 28% (mainly induced labours). These statistics reflect the severe diabetic status of the study group.

Table 1 summarizes the characteristics of the study population. The two groups were similar for maternal age and gestational ages at assessment. At the time of assessment the median Mod-MPI (with interquartile range's) were 0.38 (0.36–0.39) and 0.59 (0.45–0.62) in the control and study groups, respectively (Table 1). Figure 2 demonstrates Mod-MPI and E/A ratio Doppler tracings in abnormal cases. Figure 3 shows a scatterplot of Mod-MPI versus gestational age with linear predictions from quantile regression superimposed. Mod-MPI decreased with advancing gestational age in both control and study groups. Adjusting for gestational age, the *p*-value for the effect of group remained statistically significant ($p < 0.001$).

The fetal Doppler evaluation yielded similar results in the study and control groups (mean UA RI: 0.62 and 0.64, mean middle cerebral artery 0.85 and 0.83 and mean ductus venosus PI of 0.56 and 0.54, respectively).

Figure 4 demonstrates the distribution of Mod-MPI between normal and adverse outcomes in the study group and correlation to the 95th percentile for our normal ranges.[15] Apart from four fetuses, all cases (25) in the study group had elevated Mod-MPI's (above the 95th percentile). The median Mod-MPI's in the gestational diabetic cases with normal and adverse outcomes were 0.45 (0.39–0.46) and 0.62 (0.6–0.65), respectively, and both differed significantly from controls (both *p*-values <0.001).

Adverse outcomes were noted in 17 of the 29 fetuses in the study group (Table 2). At a cut-off MPI value of >=0.52, a

Table 1 **Characteristics of the study population [median (interquartile range)]**

	Control	Study	*p*-value
	n = 29	*n* = 29	
	Median (IQR)	Median (IQR)	
Gestational age (weeks)	35 (34–36)	35 (34–36)	1
Maternal age (years)	32 (30–33)	32 (30–33)	0.95
Gestational age at delivery (weeks)	39.43 (39–39.71)	38.35 (37.71–38.71)	<0.001
AFI (cm)	12.9 (11.9–13.8)	18.10 (16.5–23)	<0.0001
EWF (g)	2555 (2410–2698)	2771 (2564–2940)	0.004
MPI	0.38 (0.36–0.39)	0.59 (0.45–0.62)	<0.0001
IRT (ms)	36 (34–37)	58 (43–59)	<0.0001
ET (ms)	176 (175–178)	157 (150–163)	<0.0001
ICT (ms)	32 (30–33)	33 (32–35)	<0.001
EA ratio	0.76 (0.75–0.78)	0.65 (0.60–0.70)	<0.0001
Birth weight (g)	2910 (2965–3017)	3310 (3586–3850)	<0.0001

IQR, interquartile range; AFI, amniotic fluid index; EWF, expected fetal weight; MPI, myocardial performance index; IRT, isovolumetric relaxation time; ICT, isovolumetric contraction time; ET, ejection time; E/A ratio, E wave/A wave peak velocity ratio at mitral valve.

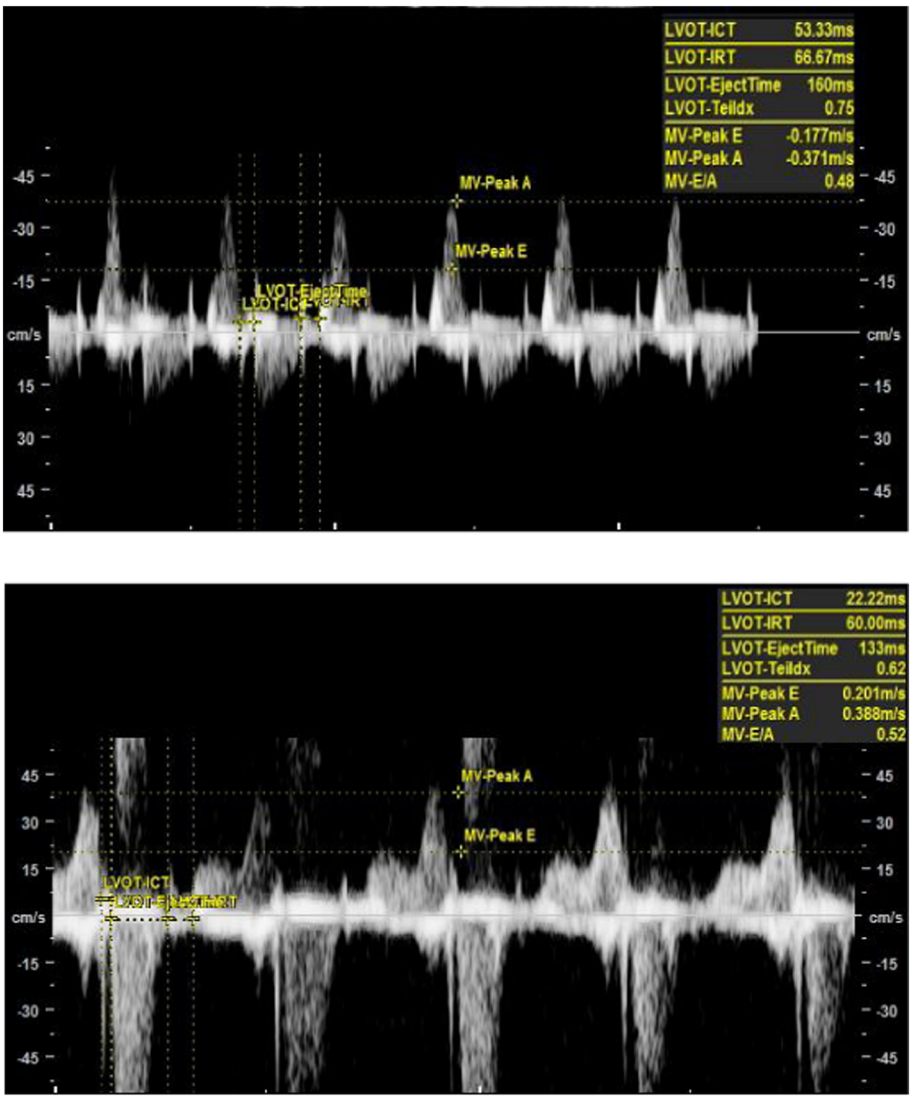

Figure 2 Abnormal myocardial performance index and E wave/A wave peak velocity ratio Doppler tracings at the mitral valve

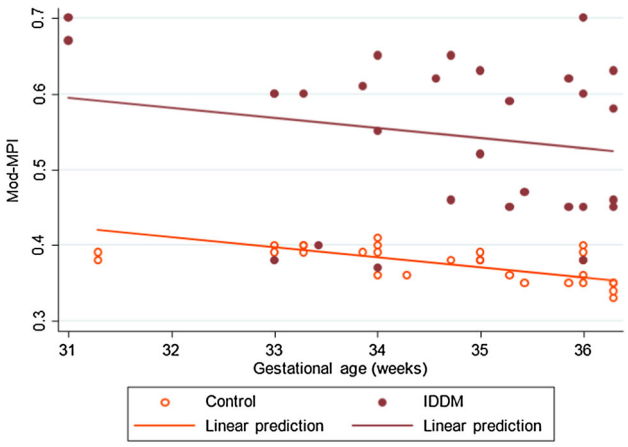

Figure 3 Scatterplot of myocardial performance index (MPI) versus gestational age with linear predictions from quantile regression superimposed. Legend: IDDM: gestational diabetic insulin dependent group (study group)

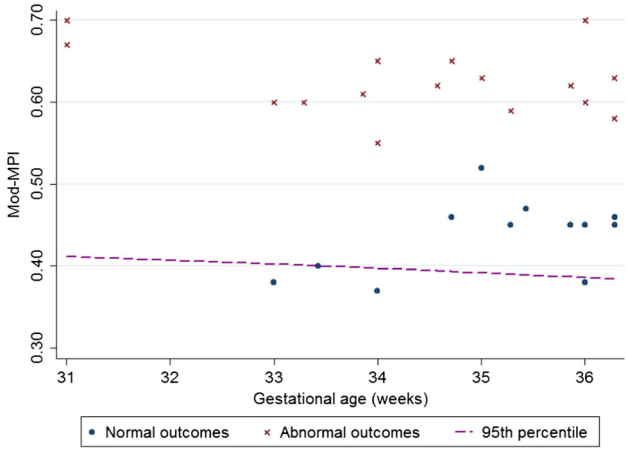

Figure 4 Distribution of myocardial performance index (MPI) between normal and abnormal outcomes in the study group and correlation to the 95th percentile from the normal ranges study[15]

Table 2 Fetal outcomes observed in study group and controls

Outcomes	Study group ($n = 29$)	Controls ($n = 29$)
Stillbirth	1	0
Neonatal death	1	0
Neonatal intensive care admission	16	0
Tachypnea + pulmonary oedema:	8	0
Neonatal cord pH <7.15	13	0
Apgars <7 (5 min)	13	0
Cardiomyopathy	1	0
Normal outcome	12	29

sensitivity of 100% [95% confidence interval (CI) 85–100%] and specificity of 92% (95% CI 70–92%) for an adverse outcome were achieved (Table 3). Special mention needs to be made of two cases of stillbirth and an early neonatal death. In the former case, the patient presented at 29 weeks with poorly controlled diabetes, severe polyhydramnios, normal umbilical RI, normal ductus venosus PI, no arterial redistribution but markedly elevated MPI at 0.70 and abnormal E/A ratio of 0.58. Cardiac Doppler data was not used in the management of the patient. The patient was admitted and closely monitored with CTG until 34 weeks when late decelerations were noted on the fetal heart rate tracing. An emergency caesarean section was performed, but unfortunately, a stillborn was delivered. The second case was assessed at 34 weeks gestation at which a mildly macrosomic fetus was noted with a normal UA RI, no arterial redistribution and normal ductus venosus PI but markedly elevated MPI at 0.67 and E/A ratio of 0.6. Cardiac Doppler data was not used in the management of the patient. The patient presented with decreased fetal movements at 36.5 weeks and CTG was found to be nonreassuring (2 days prior to admission the UA RI and CTG's were normal). The patient was delivered by caesarean section, but the neonate was asphyxiated at birth and died in the early neonatal period. Neonatal cord pH showed severe acidaemia. No adverse outcomes were noted in the control group.

Table 3 Sensitivity and specificity of modified myocardial performance index (Mod-MPI) cut-offs for adverse outcome in gestational diabetic pregnancies

Mod-MPI cut-off point	Sensitivity (%)	Specificity (%)	Classified (%)	LR+
(>=0.4)	100	25.0	69.7	1.3
(>=0.45)	100	33.3	72.4	1.5
(>=0.46)	100	66.7	86.2	3.0
(>=0.47)	100	83.3	93.1	6.0
(>=0.52)	100	91.7	96.5	12.0
(>=0.55)	100	100	100	

LR+, positive likelihood ratio.

DISCUSSION

This study has shown that the Mod-MPI is significantly increased and the E/A ratios significantly lower in fetuses of poorly controlled diabetic mothers compared with controls. The lower E/A ratio reflects diastolic dysfunction in these fetuses. The increase in the Mod-MPI was due to a decrease in ET and an increase in the IRT. The increase in the IRT corroborates the finding of the significantly lower E/A ratio in the diabetic pregnancies indicating diastolic dysfunction. The increase in IRT together with the decrease in ET, which is a marker of systolic function, reflects global myocardial dysfunction. A total of 17 out of 25 fetuses with an elevated Mod-MPI showed abnormal outcomes. Of significance in this study was that adverse outcomes appeared to be related to the severity of an abnormal MPI. A cut-off MPI value >0.52 confers a sensitivity of 100% and specificity of 92% for an adverse perinatal outcome.

A limitation of our study is the high incidence of adverse perinatal outcome in the diabetic group (58%). This was probably related to poor glycaemic control. Thus, our results may not be extrapolated to a population of better controlled diabetic patients. Moreover, cases with adverse perinatal outcome also had other risk factors, namely, higher birth weight centiles and low E/A ratios: Assessment of the independent ability of Mod-MPI to predict adverse outcomes require larger studies. Another limitation is that the Mod-MPI requires experience and training to obtain a reliable result. However, this parameter shows very good reproducibility when its evaluation is performed using specific settings with valve clicks as landmarks as shown in our study of reference intervals of the Mod-MPI in normal pregnancies.[15]

The high incidence of transitory tachypnea and/or pulmonary oedema (8 out of 17 infants) in the study group could be the result of diastolic dysfunction as reflected by the low E/A ratios and increased IRT in the study group. However, the tachypnea could also be attributed to alternate mechanisms, for example, surfactant deficiency that could occur in insulin controlled diabetics or transient tachypnea of the newborn (which can occur with caesarean delivery).

There are a number of possible explanations for the association between elevated Mod-MPI and adverse outcome. Maternal diabetes may lead to thickening of the fetal interventricular septum, which in turn can be associated with a decrease in the ratio between the peak velocities during early passive ventricular filling and active atrial filling at the level of the atrioventricular valves.[10] Impaired ventricular compliance has also been reported in fetuses of diabetic pregnancies, which could result in diastolic dysfunction.[11,16] This corroborates our finding of diastolic dysfunction as evidenced by the decreased E/A ratio and prolongation of the IRT. Furthermore, fetuses of insulin dependent diabetic pregnancies have an increased preload index in the inferior vena cava, which can be associated with a lower umbilical arterial blood pH and higher haematocrit at birth, as well as increased neonatal morbidity.[17] These findings suggest that one of the main mechanisms inducing fetal compromise in diabetic pregnancies is the development of myocardial dysfunction because of alterations of ventricular compliance in response to an abnormal metabolic milieu.

Furthermore, a powerful and critical finding in diabetic pregnancies is that significant acidaemia and hyperlacticaemia can occur in fetuses in the absence of hypoxaemia,[18–20] which may render standard monitoring models ineffective. Thus, the need to search for alternate monitoring models especially in severe diabetics.

The two cases of perinatal death in our series may point to severe myocardial dysfunction as the underlying cause of the deaths, but this needs to be corroborated in a larger study before a clear correlation can be made. What these cases do demonstrate however is the inability of CTG and UA Doppler to adequately predict fetal compromise.

Figueroa *et al.*[14] also demonstrated increased Mod-MPI in fetuses of diabetic mothers compared with controls but the increase in MPI in their study (average Mod-MPI of 0.42 in gestational diabetics and 0.45 in pregestational diabetics) was modest as compared with our study Their study group mostly comprised pregnant diabetics in the milder spectrum of disease. This would explain the milder increases in Mod-MPI in their study and would also be in line with the findings of the study of Wong *et al.*[21] and Gardiner *et al.*[22] who demonstrated a link between metabolic control during pregnancy and functional fetal heart alterations.

In conclusion, this study has documented abnormal outcomes in poorly controlled diabetic pregnancies with Mod-MPI's >=0.52. We hypothesize that elevated Mod-MPI may be due to an abnormal metabolic milieu and may be related to adverse outcomes. If confirmed, Mod-MPI would become an attractive monitoring method to detect possible fetal deterioration in the diabetic pregnancy. Our study significantly contributes to the debate of how to monitor the diabetic pregnancy. However, these results need to be corroborated in future larger prospective trials before integration into routine practice. Further studies should also address whether use of Mod-MPI to guide clinicians in timing of delivery improves perinatal outcomes.

Ethics approval

Ethical approval was obtained from the Biomedical Research Ethics Committee at the University of KwaZulu-Natal.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Fetal complications in gestational diabetes without microvascular complications are related to fetal hyperinsulinism. Our present prenatal surveillance techniques in diabetic pregnancies are neither appropriate nor sufficient as a monitoring tool. Impaired cardiac function in fetuses of diabetic pregnancies has been documented, but no link to adverse outcome has been demonstrated.

WHAT DOES THIS STUDY ADD?

- This study has established an association between fetal cardiac dysfunction and abnormal fetal outcomes in poorly controlled gestational diabetic pregnancies. There seems to be an association between severity of the myocardial performance index elevation and rates of abnormal outcomes. Myocardial performance index may be an attractive monitoring tool of the fetus in the poorly controlled diabetic pregnancy.

REFERENCES

1. Tei C, Ling LH, Hodge DO. New index of combined systolic and diastolic myocardial performance: A simple and reproducible measure of cardiac function—a study in normal and dilated cardiomyopathy. J Cardiol 1995;26:357–66.
2. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. J Cardiol 1995;26:135–6.
3. Tei C, Dujardin KS, Hodge DO. Doppler echocardiographic index for assessment of global right ventricular function. J Am Soc Echocardiogr 1996;9:838–47.
4. Friedman D, Buyon J, Kim M, *et al.* Fetal cardiac function assessed by Doppler myocardial performance index (Tei index). Ultrasound Obstet Gynecol 2003;21:33–6.
5. Raboisson MJ, Bourdages M, Fouron JC. Measuring left ventricular performance index in fetuses. Am J Cardiol 2003;91:919–21.
6. Hernandez-Andrade E, Figuero-Diesel H, Kottman C, *et al.* Gestational-age adjusted reference values for the modified myocardial performance index for evaluation of left fetal cardiac function. Ultrasound Obstet Gynecol 2007;29:321–5.
7. Salvesen DR, Brunedell JM, Proudler A, *et al.* Fetal pancreatic beta-cell function in pregnancies complicated by maternal diabetes mellitus. Am J Obstet Gynecol 1993;168:1363–9
8. Wong SF, Chan FY, Cincotta RB, *et al.* Use of umbilical artery Doppler velocimetry in the monitoring of pregnancy in women with pre-existing diabetes. Aust N Z J Obstet Gynaecol 2003;43:302–6
9. Wong SF, Petersen SG, Idris N, *et al.* Ductus venosus velocimetry in monitoring pregnancy in women with pregestional diabetes mellitus. Ultrasound Obstet Gynecol 2010;36:350–4
10. Rizzo G, Aarduini D, Romanini C. Cardiac function in fetuses of type 1 diabetic mothers. Am J of Obstet Gynecol 1991;164:837–43.
11. Rizzo G, Pietropolli A, Capponi A, *et al.* Analysis of factors influencing ventricular filling patterns in fetuses of type 1 diabetic mothers. J Perinat Med 1994;22:149–57.
12. Ichizuka K, Matsuoka R, Hasegawa J, *et al.* The Tei index for evaluation of fetal myocardial performance in sick fetuses. Early Hum Dev 2005;81:273–9
13. Tsutsumi T, Ishii M, Eto G, *et al.* Serial evaluation for myocardial performance in fetuses and neonates using a new Doppler index. Paediatric Int 1999;41:722–7.
14. Figueroa H, Silva MC, Kottman C, *et al.* Fetal evaluation of the modified-myocardial performance index in pregnancies complicated by diabetes. Prenat Diagn 2012;32:943–8.
15. Bhorat IE, Bagratee J, Reddy T. Gestational age-adjusted trends and reference intervals of the modified myocardial performance index (Mod-MPI) with its interpretation in the context of established cardiac physiological principles. Prenat Diagn DOI:10.1002/pd. 4414.
16. Weiner Z, Zloczower M, Lerner A, *et al.* Cardiac compliance in fetuses of diabetic women. Obstet Gynecol 1999;93:948–51.
17. Nicolaides KH, Rizzo G, Hecher K. Placental and Fetal Doppler. London: The Parthenon Publishing Group, 2000;128–9.
18. Bradley RJ, Brudenell JM, Nicolaides KH. Fetal acidosis and hyperlacticemia diagnosed by cordocentesis in pregnancies complicated by maternal diabetes mellitus. Diabet Med 1991;8:464–8.
19. Salvesen DR, Brudenell JM, Nicolaides KH. Fetal polycythaemia and thrombocytopaenia in pregnancies complicated by diabetes mellitus. Am J of Obstet Gynecol 1992;166:1287–92
20. Salvesen DR, Brudenell JM, Nicolaides KH. Fetal plasma erythropoietin in pregnancies complicated by maternal diabetes mellitus. Am J Obstet Gynecol 1993;168:88–94.
21. Wong ML, Wong WH, Cheung YF. Fetal myocardial performance in pregnancies complicated by gestational impaired glucose tolerance. Ultrasound Obstet Gynecol 2007;29:395–400.
22. Gardiner HM, Pasquini L, Wolfenden J, *et al.* Increased periconceptual maternal glycated haemoglobin in diabetic mothers reduces fetal long axis cardiac function. Heart 2006;92:1125–30.