Title of paper: Determination of the Myocardial Performance Index in Deteriorating Grades of Intrauterine Growth Restriction and its Link to Adverse Outcomes

Running head: Myocardial performance index in deteriorating grades of growth restriction and its link to adverse outcomes.

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What is already known about the topic

The heart plays a central role in the fetal adaptive mechanisms to placental insufficiency and hypoxia. Although increases in the myocardial performance index (MPI) have been reported in growth restricted fetuses in a number of studies, links of MPI to adverse perinatal outcomes have been sparsely reported. Furthermore no specific MPI values to adverse perinatal outcomes have been established, which is needed if it is to be a useful parameter in the clinical setting.

What does the study add to the topic

Fetal myocardial performance deteriorates with severity of growth restriction. This study has established an association between fetal cardiac dysfunction and abnormal fetal outcomes and also between severity of MPI elevation and rates of adverse outcomes in growth restriction. Specific MPI cut-offs to adverse perinatal outcome have been suggested. MPI and the E/A ratio may be an attractive monitoring tool of the fetus in severe intrauterine growth restriction.
ABSTRACT:

Aim:
To determine the fetal modified myocardial performance index (Mod-MPI) and E-wave/A-wa
wave peak velocities (E/A ratio) in deteriorating grades of intrauterine growth restriction (IUGR) and its link to adverse outcomes defined as perinatal death, hypoxic ischaemic encephalopathy, neonatal resuscitation, neonatal cord pH < 7.15, intraventricular haemorrhage and bronchopulmonary dysplasia.

Method:
Forty three pregnant women with IUGR defined as the abdominal circumference < 10th percentile for gestational age and umbilical resistance index > 2 standard deviations in the 3rd trimester of pregnancy were matched for gestational age and maternal age with 43 women with appropriate for gestational age fetuses. The IUGR group was subdivided based on multiwessel Doppler anomalies into different grades of growth restriction. Mod-MPI and E-wave/A-wave peak velocity (E/A) ratio were determined and linked to perinatal outcome.
Results:

The median Mod-MPI was significantly higher in growth-restricted fetuses compared to controls (0.59 vs 0.37, p < 0.001), and increased with severity of IUGR, the classification of which was based on degree of abnormality of the umbilical resistance index, presence of arterial redistribution and degree of abnormality of the ductus venosus (DV) Doppler indices. A cut-off Mod-MPI value of 0.54 conferred a sensitivity of 87% (CI: 66-97%), specificity of 75% (CI: 55-91%) and a likelihood ratio (LR) of 3.47 for an adverse outcome. A cut-off Mod-MPI value of 0.67 conferred a sensitivity of 100% (CI: 54-100%), specificity of 81% (CI: 65-92%) and LR of 5.28 for perinatal death. No abnormal outcomes occurred in controls. In logistic regression analysis the MPI remained a significant predictor of adverse outcome after adjusting for gestational age of delivery, fetal weight, E/A ratio, maternal age, DV Doppler indices, amniotic fluid index (AFI) and umbilical artery resistance index (Adjusted OR, 95% CI: 2.60 (1.15-5.83), p-value 0.02). MPI fared significantly better than the E/A ratio as a predictor of adverse outcome (area under the ROC curve of 0.94 and 0.76 respectively - p<0.001).
Conclusion

Fetal myocardial performance deteriorates with severity of growth restriction. There is an association between severity of the MPI elevation and rates of adverse perinatal outcome. The Mod-MPI and E/A ratio have the potential to be integrated into routine surveillance techniques of the growth restricted fetus.

Introduction

A Doppler index of combined systolic and diastolic ventricular myocardial performance, the 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\(^1,2,3\). This index is increasingly being used as a monitoring tool in fetuses to detect compromise\(^4\). The technique of acquisition in the fetus has evolved to a modified MPI (Mod-MPI), which was used in this study\(^5-7\). Our previous study has established reference intervals and trends of the MPI in normal pregnancies\(^8\). E-wave/A-wave peak velocity ratio (E/A) is also used as an indicator of ventricular diastolic function.
Fetuses with intrauterine growth restriction (IUGR) are at increased risk for adverse short and long-term outcomes\(^9\)\(^{-12}\). The heart plays a central role in the fetal adaptive mechanisms to placental insufficiency and hypoxia. Cardiac alterations in growth restricted fetuses include impaired ventricular filling (lower E/A ratios)\(^13\), lower peak velocities in the aorta and pulmonary arteries\(^14\), increased aortic and decreased pulmonary time to peak velocity\(^15\) and a relative increase of left cardiac output associated with decreased right cardiac output\(^16\), thus improving cerebral perfusion. This demonstrates the pivotal role of the heart in the compensatory mechanisms of the growth restricted fetus.

Increased MPI have been reported in growth restricted fetuses\(^{17,18,19}\). The methodology employed by Tsutsumi et al\(^17\) (two different waveform technique) in obtaining the MPI had a problem in reproducibility. Other studies\(^{18,19}\) used MPI values > 95\(^{th}\) percentile cut-off or trends as their reference for abnormality making practical clinical use of this parameter difficult due to differing trends and values of the 95\(^{th}\) percentile in different studies\(^7,8,17,20\). Association of elevated MPI to adverse perinatal outcomes have been sparsely reported. Furthermore there have been no studies linking specific MPI value cut-offs to adverse perinatal outcomes.

In this study the aim was to elucidate fetal cardiac function using the Mod-MPI and E/A ratios in delineated deteriorating grades of growth restriction to determine whether the MPI influences perinatal outcome and, if so, to establish specific MPI cut-offs for adverse perinatal outcome.
Methods

The study was approved by the Bioethics Committee of the University of Kwa-Zulu Natal.

Forty three singleton fetuses between 28 and 34 weeks gestation between December 2012 and September 2013, diagnosed with intrauterine growth restriction on ultrasound (abdominal circumference below the 10th percentile for gestational age and an abnormal umbilical artery resistance index > 2 standard deviations16) attending the Fetal Unit at Inkosi Albert Luthuli Hospital, Durban, South Africa were recruited to the study. Exclusion criteria were congenital malformations, multiple pregnancies, chromosomal anomalies, evidence of pre-eclampsia and abnormal fetal heart rates (either tachycardia or bradycardia). Forty three women with normal pregnancies were matched for gestational age and served as the control group. IUGR was categorized into 3 types, namely uncompensated, compensated and critical status IUGR, reflecting fetal response to placental insufficiency and degree of placental vascular resistance. Uncompensated IUGR was defined by the following: AC < 10th percentile for gestational age, elevated umbilical artery RI at > 2 standard deviations for gestational age with no arterial redistribution and normal venous Doppler. Compensated IUGR had in addition a middle cerebral artery RI below the 5th centile for gestational age reflecting arterial redistribution which is in effect a central cardiovascular adaptation to early hypoxia21. Critical status IUGR was defined when there was absent (AEDF) or reversed end diastolic flow (RAEDF) in the umbilical artery and/or severe venous Doppler anomalies as reflected in the finding of absent or reversed flow during atrial contraction in the ductus venosus (DV) which translates into a high suspicion of acidosis22.
Using Doppler echocardiography the mod-MPI and E/A ratios at the level of the mitral valve were determined (see below). Fetal echocardiography was performed using an E8 General Electric Voluson ultrasound system (GE Medical Systems, WI, USA) or the Siemens Antares ultrasound system (Siemens Medical systems, Malvern, PA, USA) were used. The four chamber view, outflow tract views, triple vessel view, longitudinal view of the aortic arch and ductus 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 \cite{1}(Fig 1). Three waveforms were considered for the calculation of the Mod-MPI and the average of the measurements were used. The same applied for the E/A ratio. A cross sectional image of the fetal thorax at the level of the 4-chamber view with an apical projection of the heart was obtained. The Doppler sample was opened to 3mm and placed in the internal leaflet of the mitral valve (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 degrees. E/A waveform were 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 mitral valve and aortic waveforms. The Doppler sweep velocity was set at 5cm/sec and the wall motion filter at 300Hz. The three time 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 inter- and intraobserver variability agreement (IB and JB as the operators) for the MPI and its components in our paper establishing reference intervals of the myocardial
performance index in normal pregnancies.

Sonographic data included fetal weight estimation for gestational age and amniotic fluid index. Doppler data included Mod-MPI, E/A ratio, umbilical artery resistance index, middle cerebral artery resistance index and ductus venosus pulsatility index.

The clinicians were blinded to the cardiac Doppler data. Delivery was indicated according to standard obstetric practice guidelines at our institution: reversed end diastolic flow in the umbilical artery, reversed or absent end-diastolic flow in the DV or decelerative cardiotocography > 28 weeks gestation.

Adverse perinatal outcome was defined by any of the following: perinatal death, neonatal resuscitation, hypoxic ischaemic encephalopathy, neonatal pH < 7.15, intraventricular haemorrhage, bronchopulmonary dysplasia.

**Statistical analysis**

All statistical analysis was performed using STATA/SE version 12.0 (Stata Corp, College Station, TX, USA). Spearman’s rank correlation was computed to assess the correlation between MPI and gestational age within each group. The Shapiro-Wilk \( W \)-test was used to test for normality. All skewed variables are reported as medians with inter-quartile ranges. Multivariable 50th percentile (Median) Quantile regression was used to determine whether there was a significant difference in the median Mod-MPI between growth restricted and
normal fetuses (control group) while adjusting for the effect of gestational age. A gestational age and group interaction term was included in the model. The Kruskal Wallis test was used to perform the overall comparison between the uncompensated, compensated and critical groups and the Wilcoxon rank sum test was used for pairwise differences. The sensitivity and specificity at each cutoff of the relevant predictor of adverse outcome was computed and the area under the ROC curve was computed. The method proposed by DeLong et al\textsuperscript{23} was used to test the equality of two or more correlated ROC curves. Similar analyses were conducted for death as the reference variable. Logistic regression was used to assess the MPI as a predictor of adverse outcome, adjusting for other fetal parameters, viz. fetal weight, gestational age at delivery, E/A ratio, maternal age, DV Doppler indices, AFI and umbilical artery Doppler. In the logistic regression, the umbilical artery resistance index was categorized as follows: $\leq 0.75$, $.75<UA\leq 0.80$ and $>0.8$-AEDF/RAEDF.

**Results**

The results presented below are based on 86 fetuses, 43 IUGR fetuses and 43 controls. The mean gestational age of the fetuses were 32.58 weeks with a standard deviation of 1.89. The median E/A ratios, amniotic fluid indices and fetal weights which were obtained at diagnosis were all significantly different between the Control and IUGR groups (Table 1). The median Mod-MPI was significantly higher in growth-restricted fetuses compared to controls (0.59 vs 0.37- $p < 0.001$) as shown in Table 1. There was a decrease in Mod-MPI with gestational age in the 43 normal fetuses (Spearman’s correlation coefficient -0.967, $p$
<0.0001), in line with our previous study. Within the growth restricted group there was a negative correlation between the Mod-MPI and gestational age (Spearman’s correlation coefficient -0.595, p < 0.0001). The median Mod-MPI, after adjusting for the effect of gestational age, was significantly higher in the growth restricted fetuses (p <0.001). There was a significant interaction between group and gestational age. Hence the rate of change in median MPI with increasing gestational age differed in the IUGR and control group. This relationship is illustrated in Figure 2. Figure 3 demonstrates Mod-MPI and E/A ratio Doppler tracing in an abnormal case.

Nineteen (44%) fetuses were classified as uncompensated, 10 as compensated (23%) and 14 (33%) were critical. Doppler data is demonstrated in Table 2. The critical group had the highest median Mod-MPI (Figure 4). The distribution of the Mod-MPI was significantly different between the three groups (p<0.0001). We found a statistically significant difference in the Mod-MPI for each of the following pairwise comparisons: Compensated vs Critical, Critical vs Uncompensated and Compensated vs Uncompensated (p < 0.001 in all comparisons).
The pregnancy and perinatal data are shown in Table 3. The more severe the grade of IUGR, the worse were the outcomes. Three fetuses in the compensated group and 10 in the critical status group had neonatal cord pH values < 7.15. There were no perinatal deaths in the uncompensated group, one death in the compensated group and 4 in the critical IUGR group.

MPI and the E/A ratio were assessed as predictors of adverse outcome. The area under the ROC curve for MPI and the E/A ratio was 0.94 and 0.76 respectively.

The MPI fared significantly better than the E/A ratio as a marker of adverse outcome (Figure 5), p-value 0.001

Adverse perinatal outcome was defined by any of the following: perinatal death, neonatal resuscitation, hypoxic ischaemic encephalopathy, neonatal pH<7.15, intraventricular haemorrhage and bronchopulmonary dysplasia. A cut-off of >=0.54 confers a sensitivity of 87% (95% CI:66-97%), specificity of 75% (95%CI:55 -91%) and likelihood ratio of 3.5 for an adverse outcome (Fig 6). In logistic regression analysis the MPI values were rescaled by multiplying values by 100, to facilitate the interpretation of co-efficients. The MPI remained a significant predictor of adverse outcome after adjusting for gestational age at delivery, E/A ratio, maternal age, DV Doppler indices, fetal weight, umbilical artery resistance index and AFI - (Adjusted OR, 95% CI: 2.60 (1.15-5.83), p-value 0.02).
The sensitivity and specificity of each MPI and DV cut-off for predicting perinatal death is presented in Fig 7. A cut-off MPI value of \( \geq 0.67 \) confers a detection rate of 100% (95% CI: 54-100%), specificity of 81% (95% CI: 65-92%) and likelihood ratio of 5.3 for perinatal death, with a significant ROC area under the curve of 0.97. The ROC area under the curve was 0.86 for DV. Thus both MPI and DV PIV are significant in prediction of perinatal death.

The control group had normal pregnancy outcomes with the average birthweight being 3110g.

**Discussion**

This study has shown that IUGR fetuses have significant impairment of cardiac function as demonstrated by significantly higher Mod-MPI values compared to controls on Doppler echocardiography, which is in line with other studies\(^ {17,18,19} \). In addition the E/A ratio was significantly lower in IUGR fetuses indicating diastolic dysfunction. It has been further shown that MPI values deteriorate with worsening degrees of growth restriction, with median MPI values corresponding to 0.52, 0.63 and 0.7 in uncompensated, compensated and critical status IUGR respectively. This would allow tracking of deteriorating myocardial performance in the growth restricted fetus. The increase in Mod-MPI was at the expense of all
components ie ET, IRT and ICT in the compensated and critical status groups indicating global myocardial dysfunction and mainly at the expense of the IRT and ET in the uncompensated group. A cut-off Mod-MPI value of >= 0.54 confers a sensitivity of 87%, specificity of 75% and likelihood ratio of 3.5 for an adverse outcome across the IUGR groupings whilst a cut-off MPI value of >=0.67 confers a detection rate of 100%, specificity of 81% and likelihood ratio of 5.3 for perinatal death. Both MPI and DV PIV are significant predictors of perinatal death (ROC area under the curve corresponding to 0.97 and 0.86 respectively). As predictors of adverse outcome in IUGR, the MPI fared significantly better than the E/A ratio (area under the ROC curve of 0.94 and 0.76 respectively –p<0.001).

There are many explanations as to the significant increase of the Mod-MPI in growth restricted fetuses. Cardiac flow is greatly influenced by modifications of arterial impedance to flow. Cardiac contractility may be directly impaired by hypoxaemia, while polycythaemia resulting from blood viscosity changes may alter preload. Deteriorating growth-restricted fetuses have shown that peak velocities in the pulmonary arteries and aorta as well as cardiac output gradually decline, suggesting a progressive worsening in cardiac function. This could explain deteriorating Mod-MPI’s with worsening grades of growth restriction. Prior to fetal distress there is a dramatic decrease in ventricular ejection force and impairment of cardiac filling. This was shown in our study by the decrease in ejection time,
and increased isovolumetric contraction and isovolumetric relaxation times in the critical status IUGR group. Thus the elevated Mod-MPI’s and reduced E/A ratios (which reflect diastolic function) in this study reflect the above cardiac pathophysiological changes.

Adverse pregnancy outcome increased with severity of IUGR from 26% in the uncompensated group, 60% in the compensated group and 79% in the critical group. In the critical group the high number of adverse outcomes would be due to a combination of severity of growth restriction, cardiac dysfunction most probably on the basis of hypoxaemia/acidaemia and prematurity, as the average gestational age of delivery was 30w2d. The deterioration of fetal myocardial performance would thus be an added risk factor to the severe preterm growth restricted fetus and its quantification using MPI and E/A ratios should be of clinical value. In logistic regression analysis the MPI remained a significant predictor of adverse outcome after adjusting for gestational age of delivery, fetal weight, E/A ratio, maternal age, DV Doppler indices, AFI and umbilical artery resistance index (Adjusted OR, 95% CI: 2.60 (1.15-5.83), p-value 0.02).

This study further shows that higher thresholds of the mod-MPI, i.e. \( >=0.54 \) (rather than the 95th percentile reported in most studies\(^7,8,20\)) were predictive of adverse outcome. The likely explanation is that there must be some fetal reserve which allows a “buffer coping zone” between the 95th percentile to the higher MPI threshold seen before which adverse outcomes set in. Severe outcomes were associated with deteriorating values of the MPI. This would be in line with the study by Crispi et al\(^18\) who demonstrated biochemical
evidence of myocardial cell damage (increasing B-type natriuretic peptide [BNP] and heart-fatty acid binding protein[H-FABP]) with haemodynamic compromise of growth restricted fetuses. Our study also demonstrated that the mod-MPI becomes abnormal early in the growth restricted process which would allow the clinician to track cardiovascular deterioration of the growth restricted fetus. Hernandez-Andrade et al\textsuperscript{19} demonstrated that the MPI was independently associated with perinatal mortality but used MPI values > 95\textsuperscript{th} percentile as the reference for abnormality rather than specific cut-off values.

Ductus venosus Doppler sonography is regarded as the gold standard for fetal monitoring and timely delivery\textsuperscript{26}, but also a late sign of fetal compromise which is often associated with fetal acidemia, myocardial necrosis and perinatal death\textsuperscript{24,27,28}. Ductus venosus Doppler can thus not be regarded as optimal in establishing timing of delivery as significant morbidity may have already set in. By tracking mod-MPI values, the clinician may determine milder stages of hypoxaemia/acidemia, which could be used in conjunction with standard monitoring models to improve prediction and pre-empt adverse outcomes.

In conclusion this study demonstrates that the mod-MPI worsens with deteriorating grades of growth restriction and suggests specific cut-off Mod-MPI values for adverse fetal outcomes, including perinatal death. It needs to be noted that these values are much higher than the 95\textsuperscript{th} percentile levels reported in most studies\textsuperscript{7,21} including our normal ranges study\textsuperscript{8} (fetal reserve that allows a “buffer coping zone” may be operational in this regard). Thus the 95\textsuperscript{th} percentile as the reference anomaly point for the MPI in IUGR may need to be re-looked. In logistic regression analysis, the MPI remained a significant predictor of adverse outcome after adjusting for other fetal parameters. The cut-off MPI values in
prediction of adverse perinatal outcome in this study need to be corroborated in future larger prospective trials and if confirmed may lead to the establishment of an MPI value-based grading or scoring system for IUGR, which could be used in conjunction with standard monitoring techniques to assist the clinician in timeous delivery of the growth restricted fetus.

The main limitation of the study are the small numbers in the groups of IUGR under investigation but the results nonetheless highlight the great potential of cardiac Doppler as an important adjunct to the standard monitoring models in the growth restricted fetus and makes the case to corroborate these findings in larger trials. Another limitation of the study 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 we have demonstrated in our study establishing reference intervals of the MPI in normal pregnancies.
References


**Table 1: Demographic, Sonographic Data and Cardiac Doppler Data between Control and Study Groups:**

Legend: AFI, amniotic fluid index; EWF, expected weight of fetus; E/A ratio, E-wave/A-wave peak velocity ratio at the mitral valve; MPI, myocardial performance index

<table>
<thead>
<tr>
<th></th>
<th>Control (n=43)</th>
<th>IUGR (n=43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (mean(SD))</td>
<td>29.62 (3.61)</td>
<td>29.67(3.59)</td>
<td>0.9535</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>33 (31-34)</td>
<td>33 (31-34)</td>
<td>1</td>
</tr>
<tr>
<td>Gestational age of delivery (mean SD)</td>
<td>39.20 (0.45)</td>
<td>36.76 (1.18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AFI (cm)</td>
<td>12.8 (12.2 - 13.4)</td>
<td>8.95 (7.95 - 10.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EWF (g)</td>
<td>2214 (1788 – 2436)</td>
<td>1559.5 (1042 - 1897.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.79 (0.78-08)</td>
<td>0.63 (0.57-0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median MPI (IQR)</td>
<td>0.37 (0.36-0.38)</td>
<td>0.59 (0.52-0.69)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 2: Doppler Data in Controls and Deteriorating Grades of Growth Restriction

Legend : AEDF, absent end diastolic flow ; REDV, reversed end diastolic flow; MPI, myocardial performance index; RI, resistance index; PIV, pulsatility index; ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; ET, ejection time

<table>
<thead>
<tr>
<th></th>
<th>Controls n=43</th>
<th>Uncompensated n= 19</th>
<th>Compensated n= 10</th>
<th>Critical Status n=14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median MPI (IQR)</td>
<td>0.37 (0.36-0.38)</td>
<td>0.52 (0.50-0.54)</td>
<td>0.63 (0.6-0.65)</td>
<td>0.70 (0.70-0.73)</td>
</tr>
<tr>
<td>Median Umbilical Artery RI (IQR)</td>
<td>0.62 (0.59-0.65)</td>
<td>0.74 (0.7-0.78)</td>
<td>0.79 (0.76 – 0.83)</td>
<td>AEDF -11 REDV -3</td>
</tr>
<tr>
<td>Median Middle Cerebral Artery RI (IQR)</td>
<td>0.86 (0.82-0.89)</td>
<td>0.85 (0.81-0.88)</td>
<td>0.62 (0.60-0.65)</td>
<td>0.58 (0.55-0.62)</td>
</tr>
<tr>
<td>Median Ductus Venosus PIV (IQR)</td>
<td>0.52 (0.48-.56)</td>
<td>0.53 (0.48- 0.58)</td>
<td>0.55 (0.50-0.6)</td>
<td>Absent a wave - 2 Rest (n=12): 0.85 (0.75-0.95)</td>
</tr>
<tr>
<td>ICT (meanSD)ms</td>
<td>28 (2.1)</td>
<td>32(0)</td>
<td>34.3</td>
<td>38.46</td>
</tr>
<tr>
<td>IRT (mean SD)ms</td>
<td>40 (2.3)</td>
<td>49.55 (2.35)</td>
<td>58.6(3.97)</td>
<td>67.74(2.60)</td>
</tr>
<tr>
<td>ET (mean SD)ms</td>
<td>171 (1.4)</td>
<td>158.35 (2.60)</td>
<td>151.4 (2.91)</td>
<td>147 (4.45)</td>
</tr>
</tbody>
</table>
Table 3: Pregnancy and Perinatal Outcomes

Legend: MPI, myocardial performance index, C/S= caesarean section, HIE=hypoxic ischaemic encephalopathy, IVH, intraventricular haemorrhage, BPD, bronchopulmonary dysplasia. In the groups below some fetuses exhibited more than one complication.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Uncompensated</th>
<th>Compensated</th>
<th>Critical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (n)</td>
<td>43</td>
<td>19</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Gest age – mean (delivery)</td>
<td>39w4d (38w3d-40w3d)</td>
<td>37w1d (36w-37w5d)</td>
<td>35w6d (34w3d-36w3d)</td>
<td>30w2d (29w5d-32w1d)</td>
</tr>
<tr>
<td>Median MPI</td>
<td>0.37 (0.36-0.38)</td>
<td>0.52 (0.50-0.54)</td>
<td>0.63 (0.6-0.65)</td>
<td>0.7 (0.7-0.73)</td>
</tr>
<tr>
<td>Mode of Delivery C/S (%)</td>
<td>6</td>
<td>35</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>Birth Weight (g)</td>
<td>3110 (2960-3476)</td>
<td>2156 (1890-2314)</td>
<td>1910 (1623-2118)</td>
<td>920 (850-1103)</td>
</tr>
<tr>
<td>5-min APGAR &lt;6</td>
<td>-</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Perinatal Deaths</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>HIE</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Neonatal Resuscit</td>
<td>-</td>
<td>5</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Cord pH &lt;7.15</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>IVH</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>BPD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>Adverse outcome</td>
<td>0%</td>
<td>26%</td>
<td>60%</td>
<td>79%</td>
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</table>
Figure 1: Normal myocardial performance index and E wave/A wave peak velocity ratio Doppler tracing at the mitral valve.
Figure 2: Interaction of Mod-MPI in Study (IUGR) Group and Controls with gestational age

Legend: Mod-MPI, modified myocardial performance index; IUGR, intra-uterine growth restriction
Figure 3: Abnormal myocardial performance index and E wave/A wave peak velocity ratio Doppler tracing at the mitral valve
Figure 4: Distribution of Mod-MPI in each of the IUGR grades

Legend: Mod-MPI, modified myocardial performance index; IUGR, intra-uterine growth restriction
Figure 5: MPI and E/A ratio as markers of adverse outcome
Figure 6: ROC curve: Significant relationship between MPI and Adverse Outcome (area under the curve of 0.94).

Legend: MPI, myocardial performance index
Figure 7: ROC curve comparing Mod-MPI and DV PIV in prediction of perinatal mortality, both being significant predictors.

Legend: Mod-MPI, modified myocardial performance index; DV PIV, ductus venosus pulsatility index