The clinical prognostic significance of myocardial performance index (MPI) in stable placental-mediated disease

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Abstract

Aim: To determine whether a single elevated myocardial performance index (MPI) value in the third trimester of pregnancy is a marker for later adverse obstetric outcomes in stable placental-mediated disease, defined as well-controlled pre-eclampsia (PE) on a single agent and/or uncompensated intra-uterine growth restriction (IUGR).

Methods: Fifty-five foetuses whose mothers had stable placental-mediated disease, either mild pre-eclampsia controlled on a single agent, and/or uncompensated IUGR in the third trimester, attending the Foetal Unit at Inkosi Albert Luthuli Hospital, Durban, South Africa were prospectively recruited with 55 matched controls. Recorded data for the subjects included demographic data of maternal age and parity, sonographic data of estimated foetal weight (EFW) and amniotic fluid index (AFI), myocardial performance index (MPI), and foetal Doppler data of the umbilical artery (UA), middle cerebral artery (MCA) and ductus venosus (DV).

Results: The mean gestational age in the controls, the IUGR and any PE cases was 31.4, 31.8 and 31.0 weeks, respectively. The distribution of MPI values was significantly lower in the controls compared to all other groups. The highest standardised MPI values were observed in the PE–IUGR group, where a median of 5.62 was observed. The only significant differences observed between the PE and IUGR groups was the UA resistance index ($p = 0.01$), where the IUGR cases tended to have higher UA values compared to the combined PE group. Borderline statistical significance was observed for the MCA resistance index values ($p = 0.05$) between these groups. The overall adverse event rate in the cases was 49%. The highest rate was observed in the PE + IUGR group, where eight out of 12 (67%) experienced adverse events. MPI *z*-scores served as a good marker of adverse events, as evidenced by the total area under the curve (AUC) of 0.90 on the ROC curve. A cut-off value of 4.5 on the MPI *z*-score conferred a sensitivity of 89% and specificity of 68% for an adverse event later in pregnancy. In univariate logistic regression, MPI *z*-score, AFI, EFW, UA Doppler, CPR category, DV Doppler and MCA Doppler were assessed separately as potential predictors of adverse outcome. The only significant predictor of adverse outcome was MPI *z*-score.

Conclusion: A single elevated value of the MPI (*z*-score > 4.5) in the third trimester in stable placental-mediated disease was a strong indicator of adverse obstetric outcomes later in pregnancy. This has the potential to be incorporated in conjunction with standard monitoring models in stable placental-mediated disease to predict an adverse event later in pregnancy and thus to reduce perinatal morbidity and mortality.

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The myocardial performance index (MPI) is a potentially useful predictor of global cardiac function.[1-3] Our previous study established normal reference ranges of modified MPI in the second half of pregnancy and interpreted the findings in the context of cardiac physiological principles.[4] Our previous studies have also suggested cut-off MPI values for adverse neonatal outcome in both growth restriction and pre-eclampsia,[5,6] and shown it to be a useful predictor of adverse foetal outcomes in other high-risk obstetric conditions.[7] MPI is defined as the sum of the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by the ejection time (ET). The equation is MPI = ICT + IRT/ET.

Placental-mediated disease, which is an umbrella term for describing different clinical phenotypes, including intra-uterine growth restriction (IUGR), pre-eclampsia (PE) and abruptio placentae, arises from a single pathophysiological event in the first trimester relating to placental maladaptation and lack of vascular remodelling of the spiral arterioles.[8,9] In early-onset pre-eclampsia (EO-PE), interstitial trophoblastic invasion is downregulated while endovascular trophoblastic invasion is limited to the decidua.

The clinical phenotype of PE represents a worse placental pathological state than IUGR, with combined phenotypes representing, in addition, obstructive vascular lesions in the placental vasculature. The sentinel event for EO-PE, EO-IUGR and combined phenotypes relates to placental maladaptation in the first trimester.[8] Therefore EO-PE, IUGR and combined phenotypes can be considered as the same pathophysiological process with differing degrees of pathological severity.

The heart plays a central role in the foetal adaptive mechanisms to placental insufficiency and hypoxia. Significant alterations

in echocardiographic parameters and elevated levels of atrial and B-type natriuretic peptides have been reported in small-for-date foetuses.[10-13] Our previous study has shown significant impairment of cardiac function in growth-restricted foetuses, with the myocardial performance deteriorating with the severity of growth restriction, as evidenced by increasing MPI values.[5] The MPI was noted to be abnormal before hypoxia or acidosis set in and can therefore be regarded as a 'warning' parameter of impending compromise. In severe pre-eclampsia it has been shown that foetal cardiac function was significantly impaired and deteriorated with worsening degrees of placental vascular resistance.[6]

This project is a continuation of our group's quest to further define the clinical use of the MPI in high-risk obstetric conditions and find its appropriate place in antenatal foetal surveillance, in the context of present standard foetal-monitoring models. With this background, the study sought to establish whether a single elevated MPI value in the third trimester in what can be deemed stable placental-mediated disease, that is, uncompensated IUGR or well-controlled pre-eclampsia (single agent and no multi-systemic manifestation) is a predictor of adverse obstetric outcome later in the pregnancy.

Methods

Fifty-five foetuses with mothers having stable placental-mediated disease, either mild pre-eclampsia controlled on a single agent and/or uncompensated IUGR in the third trimester, attending the Foetal Unit at Inkosi Albert Luthuli Hospital, Durban, South Africa were consecutively prospectively recruited. There were 55 matched controls. This study was approved by the Biomedical Research Ethics Committee of the University of Kwa-Zulu Natal, Durban, South Africa (BE228/12).

Uncompensated IUGR was defined as follows: abdominal circumference < 10th percentile for gestational age, positive flow in the umbilical artery but resistance index more than two standard deviations (2SD) above the mean with no arterial redistribution, and normal venous Doppler, that is, a non-hypoxic, non-acidotic growth-restrictive state. Foetuses with absent or reversed end-diastolic flow in the umbilical artery were excluded.

Mild pre-eclampsia was defined by the criteria as set out by the American College of Obstetricians and Gynaecologists[14] as systolic blood pressure ≥ 140 mmHg and < 150 mmHg, or diastolic blood pressure ≥ 90 mmHg and < 100 mmHg on two occasions at least six hours apart in a woman on bed rest. This is accompanied by a proteinuria reading of 1–2+ on dipstick testing on two random samples at least six hours apart.

All cases of oliguria (< 500 ml of urine in 24 hours), cerebral or visual disturbances, pulmonary oedema, epigastric pain, impaired liver function and thrombocytopaenia representing unstable/severe pre-eclampsia at the time of assessment were excluded. Other exclusion criteria were congenital malformations, multiple pregnancies, foetuses of diabetic mothers, foetuses of mothers treated with a tocolytic agent, and foetuses with abnormal heart rates (tachycardia or bradycardia).

Data recorded for subjects included demographic data of maternal age and parity, sonographic data of foetal weight and amniotic fluid index, cardiac Doppler data of MPI, and foetal Doppler data of umbilical artery (UA), middle cerebral artery (MCA) and ductus venosus (DV). The cerebro-placental ratio (CPR) was calculated and plotted on the Ebbing graph to determine the percentile.[15]

Foetal echocardiography using the E8 Voluson General Electric 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 and ductal arch, and colour-flow mapping were used to screen for cardiac malformations. The MPI was calculated in the foetal left ventricle[4,16] (Fig. 1). Our previous study established reference intervals and trends of the MPI in normal pregnancies and the methodology of obtaining the MPI has been described in detail in the article.[4] A cross-sectional image of the foetal 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 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 was always displayed as positive flow. The Doppler gain was lowered as far as possible to clearly visualise the echoes corresponding to the opening and closing clicks of the two valves at the beginning and end of the E/A (mitral valve) and aortic waveforms. Cruz-Martinez *et al.*[17] suggested using the beginning of the mitral and aortic valve clicks as the landmarks for measurement but this can lead to poorer variability and varying results due to variation in valve click widths.

Measurement of the time intervals at the peak of the valve clicks was used as it overcomes this problem, and is more precisely definable than the base, as was performed in our normal reference values study, showing excellent reproducibility,[4] and also as suggested by Meriki *et al.*[18] This is a clearer landmark and overcomes variations in valve click width and has a better reproducibility.

The Doppler sweep velocity was set at 5 cm/s and the wall motion filter at 300 Hz. The three time periods were estimated as follows: ICT – from the beginning of the MV closure to the AV opening; ET – from the AV opening to closure; IRT – from AV closure to MV opening. The modified MPI (Mod-MPI) = (ICT + IRT)/ET. The peak of the click was used as the landmark, as suggested by Meriki *et al.*,[18] as this results in better reproducibility.

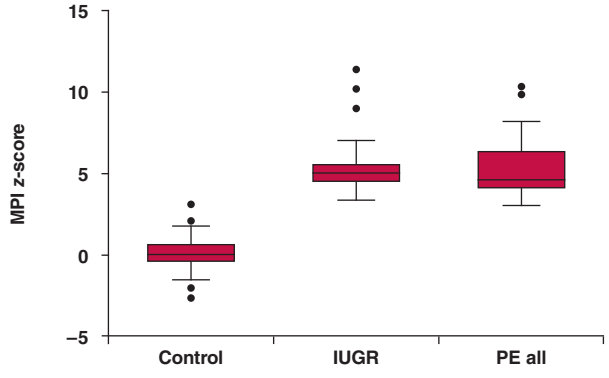

Fig. 1. MPI *z*-score versus controls, IUGR and PE group.

Table 1. Foetal parameters stratified by group

Parameters	*Controls (n = 55)*	*IUGR (n = 32)*	*PE (n = 23)*	p-*value any PE vs IUGR*	*PE-only (n = 11)*	*PE–IUGR (n = 12)*	p-*value IUGR vs controls*	p-*value* PE-only vs controls	p-*value* PE–IUGR vs controls
UA	0.67 (0.66–0.69)	0.76 (0.745–0.79)	0.68 (0.66–0.75)	0.0108	0.67 (0.66–0.69)	0.715 (0.665–0.78)	< 0.0001	0.8189	0.0639
Gestation age (weeks), mean (SD)	31.44 (1.88)	31.77 (1.65)	31.01 (1.90)	0.231	31.70 (1.53)	30.37 (2.04)	0.4079	0.6670	0.0831
MPI	0.38 (0.37–0.39)	0.535 (0.485–0.595)	0.50 (0.47–0.59)	0.3556	0.48 (0.45–0.49)	0.55 (0.50–0.60)	< 0.0001	< 0.0001	< 0.0001
MPI *z*-score	–0.01 (–0.38–0.38)	5.00 (4.37–5.58)	4.57 (4.07–6.32)	0.7200	4.29 (3.54–4.57)	5.62 (4.71–7.82)	< 0.0001	< 0.0001	< 0.0001
MCA	0.83 (0.82–0.86)	0.80 (0.78–0.83)	0.83 (0.80–0.86)	0.0538	0.83 (0.81–0.85)	0.82 (0.79–0.86)	0.0008	0.4940	0.2752
AFI	13 (12–14.5)	12.1 (10.7–13)	12 (11.1–13)	0.6944	11.8 (11.1–12.3)	12.65 (11.35–13.1)	0.007	0.0019	0.2324
EFW (mg)	2005 (1717–2210)	1561.5 (1344–1676)	1767 (1305–1989)	0.1105	1989 (1655–2012)	1600.5 (1076.5–1800.5)	< 0.0001	0.3482	0.0010

UA = umbilical artery, MPI = myocardial performance index, MCA = middle cerebral artery, AFI = amniotic fluid index, EFW = estimated foetal weight. Data are reported as median (IQR) unless otherwise stated.

All the pre-eclamptic mothers were controlled on single agents and none had magnesium sulphate therapy before our examination. Steroids were not administered to the patients at the time of the assessment. At least three measurements were taken once a clear and consistent Doppler trace had been obtained, and the measurement taken from the clearest waveform was included in the final analysis.

Adverse obstetrical outcome later in the pregnancy was defined as: development of significant oligohydramnios (AFI < 5 cm), antenatal decelerative cardiotocography, intra-uterine death, development of imminent eclampsia or HELLP (haemolysis, elevated liver enzymes and low platelet count) syndrome, abruption placentae, and deterioration of foetal Dopplers (arterial redistribution or venous Doppler anomalies).

We have previously documented high levels of inter- and intra-observer variability agreement for the MPI and its components in our article establishing reference intervals of the MPI in normal pregnancies.[4]

Statistical analysis

MPI values were transformed to *z*-scores using the standards proposed by Bhorat *et al*.[4] Continuous variables are reported as means with standard deviations for normally distributed variables, and medians with interquartile ranges for variables with skewed distributions. The Shapiro–Wilk test was used to test for normality. The Wilcoxon rank sum test was used to perform comparisons of the foetal parameters between the study groups. To compare the adverse event rate and CPR categories between the study groups, Fisher's exact test was used.

The overall diagnostic accuracy of the MPI *z*-score for adverse outcomes was assessed through computation of the area under the receiver operating characteristics (ROC) curve. To determine whether the MPI was an independent predictor of adverse outcome, while adjusting for other foetal parameters, logistic regression was used; *p*-values less than 0.05 were considered statistically significant. All analysis was performed in Stata version 14 (Stata Corp, College Station, TX, USA).

Results

A total of 55 subjects, comprising 32 IUGR cases, 11 PE-only cases and 12 PE with IUGR cases (total PE cases: 23) were included in the analysis. Controls were matched to cases in a 1:1 ratio by gestational age rounded off to the nearest week. The mean gestational age in the controls, IUGR and any PE cases was 31.4, 31.8 and 31.0 weeks, respectively.

The UA resistance index (UA RI) values were significantly lower in the controls compared to the IUGR cases ($p < 0.0001$). There was no significant difference in the median UA RI between the controls and PE-only cases ($p = 0.819$). The amniotic fluid index (AFI) was significantly higher in the controls compared to the IUGR and PE-only group ($p = 0.007$ and 0.002, respectively). MCA resistance index (MCA RI) values were significantly higher in the controls compared to the IUGR-only cases, however no significant difference was observed between the controls and PE-only and PE–IUGR cases, respectively. The lowest estimated foetal weight (EFW) was observed in the IUGR cases, followed by the PE–IUGR cases. No significant differences were observed between the EFW in the controls and PE-only cases ($p = 0.348$).

The distribution of the standardised MPI values between the groups of interest is presented in Table 1 and Figs 1 and 2. It is clear that the distribution of MPI values was significantly lower in the controls compared to all other groups. This is affirmed by the analysis in Table 1, with all differences statistically significant. The highest standardised MPI values were observed in the PE–IUGR group, where a median of 5.62 was observed (Fig. 2).

All foetal parameters were compared between the PE group combined ($n = 23$) and IUGR cases ($n = 32$). The only significant differences observed between these two groups was the UA ($p = 0.01$), where the IUGR cases tended to have higher UA values compared to the combined PE group. Borderline statistical significance was observed for the MCA values ($p = 0.05$) between these groups.

The overall adverse event rate in the cases was 49%, which is shown in Fig. 3 and Table 2. The highest rate was observed in the PE–IUGR group where eight out of 12 (67%) experienced adverse events. There was no significant difference in the adverse event rate between the three groups (0.197).

Foetuses were also categorised according to their CPR percentile for gestational age; 81, 9 and 58% were observed to have CPR values less than the fifth percentile in the IUGR,

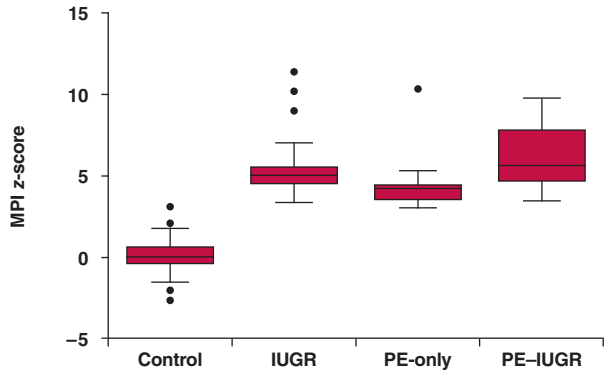

Fig. 2. Mpi *z*-score versus controls, IUGR, PE-only and PE + IUGR groups.

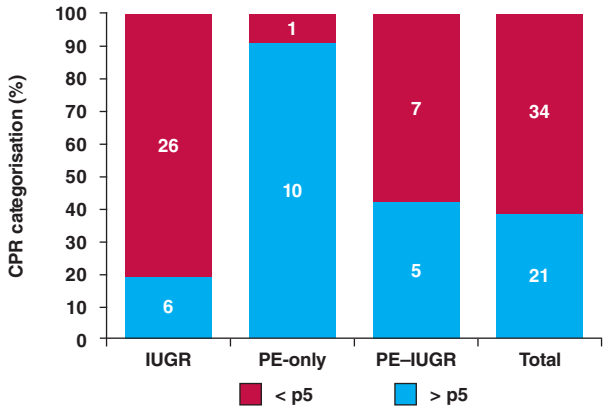

Fig. 4. CPR categorisation between groups.

PE-only and PE–IUGR groups, respectively (Fig. 4). This difference was statistically significant ($p < 0.001$).

The utility of MPI in predicting adverse outcomes was assessed. We found that the MPI *z*-scores served as a good marker of an adverse obstetric event later in pregnancy, as evidenced by the total area under the curve (AUC) of 0.90. The ROC curve is presented in Fig. 5. A cut-off value of 4.5 on the MPI *z*-score conferred a sensitivity of 89% and specificity of 68% (Table 3).

We also assessed the accuracy of a CPR value less than the fifth percentile in predicting adverse outcomes. Fig. 4 demonstrates CPR categorisation between the groups. Table 4 demonstrates the utility of CPR in predicting adverse outcomes. Of the 54 cases with CPR values, 33 (61%) had values less than the fifth percentile (p5). The sensitivity of CPR < p5 in predicting adverse events was 66% and the specificity was estimated at 42% (Table 4).

Logistic regression was performed to evaluate predictors of adverse events after adjusting for all other foetal parameters. In univariate logistic regression, MPI *z*-score, AFI, EFW, UA Doppler, CPR category, DV Doppler and MCA Doppler were assessed separately as potential predictors of adverse outcomes. The only significant predictor of adverse outcome was the MPI *z*-score. Treating this as a continuous variable, the odds ratio was 7.8 (95% CI: 2.3–26.1), which can be interpreted as follows: for a one unit higher Mod-MPI *z*-score, there is an approximately eight-times higher risk of an adverse outcome.

Table 2. CPR versus adverse events

	IUGR	*PE-only*	*PE–IUGR*	*Total*	p-*value*
Adverse events, *n* (%)	16 (50)	3 (27)	8 (67)	27 (49)	0.197
CPR					< 0.001
> p5	6 (19)	10 (91)	5 (42)	21 (38)	
< p5	26 (81)	1 (9)	7 (58)	34 (62)	

CPR = cerebro-placental ratio, IUGR = intra-uterine growth restriction, PE = pre-eclampsia.

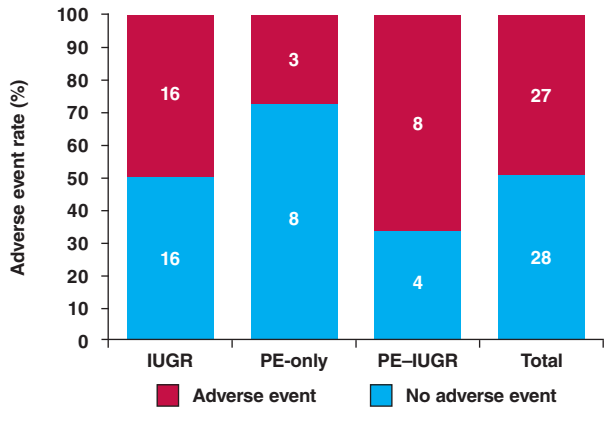

Fig. 3. Adverse-event rate between groups.

Discussion

We have previously shown that mainly in severe IUGR, that is, compensated and critical-status IUGR and in severe early-onset pre-eclampsia, an elevated MPI was a good predictor of adverse neonatal outcome, and cut-off MPIs were suggested.[5,6] This study now focused on whether an elevated MPI in milder forms of placental-mediated disease was a predictor of adverse obstetric outcome later on in the pregnancy. This study has shown that a cut-off value of 4.5 on the MPI *z*-score is a strong indicator of adverse obstetric outcome later in pregnancy, with

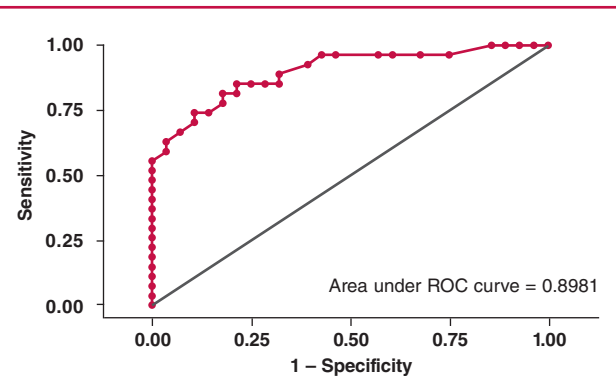

Fig. 5. ROC curve depicting diagnostic accuracy of MPI *z*-scores.

Table 3. MPI *z*-score cut-off points for predicting adverse outcomes

Cut-off point	*Sensitivity (%)*	*Specificity (%)*	*Correctly classified (%)*	*LR+*	*LR–*
(≥ 2.98)	100.00	0.00	49.09	1.0000	
(≥ 3.23)	100.00	3.57	50.91	1.0370	0.0000
(≥ 3.27)	100.00	7.14	52.73	1.0769	0.0000
(≥ 3.53)	100.00	10.71	54.55	1.1200	0.0000
(≥ 3.54)	100.00	14.29	56.36	1.1667	0.0000
(≥ 4.07)	96.30	25.00	60.00	1.2840	0.1481
(≥ 4.15)	96.30	32.14	63.64	1.4191	0.1152
(≥ 4.16)	96.30	39.29	67.27	1.5861	0.0943
(≥ 4.29)	96.30	42.86	69.09	1.6852	0.0864
(≥ 4.31)	96.30	53.57	74.55	2.0741	0.0691
(≥ 4.45)	96.30	57.14	76.36	2.2469	0.0648
(≥ 4.49)	92.59	60.71	76.36	2.3569	0.1220
(≥ 4.5)	88.89	67.86	78.18	2.7654	0.1637
(≥ 4.58)	85.19	67.86	76.36	2.6502	0.2183
(≥ 4.64)	85.19	71.43	78.18	2.9815	0.2074
(≥ 4.67)	85.19	75.00	80.00	3.4074	0.1975
(≥ 4.83)	85.19	78.57	81.82	3.9753	0.1886
(≥ 4.89)	81.48	78.57	80.00	3.8025	0.2357
(≥ 4.97)	81.48	82.14	81.82	4.5630	0.2254
(≥ 5.11)	77.78	82.14	80.00	4.3556	0.2705
(≥ 5.23)	74.07	85.71	80.00	5.1852	0.3025
(≥ 5.24)	74.07	89.29	81.82	6.9136	0.2904
(≥ 5.29)	70.37	89.29	80.00	6.5679	0.3319
(≥ 5.35)	66.67	92.86	80.00	9.3333	0.3590
(≥ 5.48)	62.96	96.43	80.00	17.6296	0.3841
(≥ 5.54)	59.26	96.43	78.18	16.5926	0.4225
(≥ 5.62)	55.56	100.00	78.18		0.4444
(≥ 5.69)	51.85	100.00	76.36		0.4815
(≥ 5.76)	48.15	100.00	74.55		0.5185
(≥ 5.77)	44.44	100.00	72.73		0.5556
(≥ 6.32)	40.74	100.00	70.91		0.5926
(≥ 6.96)	37.04	100.00	69.09		0.6296
(≥ 7.08)	33.33	100.00	67.27		0.6667
(≥ 7.69)	29.63	100.00	65.45		0.7037
(≥ 7.95)	25.93	100.00	63.64		0.7407
(≥ 8.15)	22.22	100.00	61.82		0.7778
(≥ 8.98)	18.52	100.00	60.00		0.8148
(≥ 9.84)	14.81	100.00	58.18		0.8519
(≥ 10.19)	11.11	100.00	56.36		0.8889
(≥ 10.33)	7.41	100.00	54.55		0.9259
(≥ 11.36)	3.70	100.00	52.73		0.9630
(> 11.36)	0.00	100.00	50.91		1.0000

LR+ = likelihood ratio positive, LR– = likelihood ratio negative.

Table 4. The utility of CPR in predicting adverse outcomes

	Adverse outcome	*No adverse outcome*
CPR < p5	18	16
CPR > p5	9	12

Sensitivity (%)	66.7
Specificity (%)	42.9
PPV (%)	52.9
NPV (%)	57.1

CPR = cerebro-placental ratio, PPV = positive predictive value, NPV = negative predictive value.

a sensitivity of 89% and specificity of 68% (AUC on the ROC curve of 0.9).

In univariate logistic regression, MPI *z*-score, AFI, EFW, UA Doppler, CPR category, DV Doppler and MCA Doppler were assessed separately as potential predictors of adverse outcome. The only significant predictor of adverse outcome was MPI *z*-score. Treating this as a continuous variable, the odds ratio was 7.8 (95% CI: 2.3–26.1), which can be interpreted as follows: for a one unit higher MPI *z*-score, there is an approximately eight times higher risk of adverse outcomes. This study suggests that even in stable placental-mediated disease, an elevated MPI can be a predictor of adverse outcome later in the pregnancy.

Our previous study and other studies[5,19,20] have shown that the MPI becomes abnormal much earlier than arterial redistribution, and DV anomalies and MPIs deteriorated with worsening grades of growth restriction. This study expands the notion that cardiac dysfunction is probably the initial quantitative parameter to become abnormal in placental-mediated disease and tracks the severity of it. It is the first study to have shown that a single elevated MPI in the context of a perceived mild/stable placental-mediated disease scenario can be predictive of deterioration later in the pregnancy.

In the study group (across all groups), adverse outcomes were reported in 49% of cases, including three intra-uterine deaths, 11 cases eventually having decelerative tococardiography, four who subsequently developed imminent eclampsia, two with HELLP syndrome, five who developed severe oligohydramnios later in the pregnancy, and two abruptios, with the highest number recorded in the PE + IUGR group (67%). This would be consistent with a more advanced placental maladaptive process.

The question is why would this be the case? Intrinsic cardiac function plays a pivotal role in the compensatory mechanisms of the growth-restricted foetus. Cardiac flow and cardiac contractility may be directly impaired by early hypoxaemia before Doppler changes in MCA can occur, while polycythaemia resulting from blood viscosity changes may alter preload.[21,22] Elevated MPIs beyond 'buffer coping zones' may be reflecting early hypoxaemia and therefore could predict adverse obstetric outcome.[5] Pre-eclampsia on the other hand affects foetal cardiac function by causing an increase in afterload. This is due to the abnormal placental remodelling process and reduced placental perfusion, causing placental vessel injury and placental vasoconstriction, leading to increased placental vascular resistance and thus increased foetal cardiac afterload. This process can certainly impact on cardiac function.

Our initial study investigating MPI in severe pre-eclampsia demonstrated that MPIs deteriorate, with worsening placental vascular resistance in severe pre-eclampsia and this was linked to adverse neonatal outcomes.[6] This is probably on the basis of angiogenic disparity, tipped in favour of anti-angiogenic substances such as soluble fms-like tyrosine kinase (sFlt-1), which are able to block the effects of vascular endothelial growth factor and placental growth factor (PLGF) by inhibiting interactions with its receptors, leading to widespread vasoconstriction.[23-26] Therefore elevation of MPI would reflect these pathophysiological mechanisms, which would directly impact on the foetal heart.

An abnormal CPR (< p5) for gestational age has been reported to be an indicator of foetal hypoxaemia and impaired long-term neurological outcome.[27] Foetuses were therefore also

categorised according to their CPR percentile for gestational age and we assessed the accuracy of a CPR value less than the fifth percentile in predicting adverse outcome. Of the 54 cases with CPR values, 33 (61%) had values less than the fifth percentile.

The sensitivity of CPR < p5 in predicting an adverse event was 67% and the specificity was estimated at 43%, which cannot be regarded as a good predictor for adverse outcome. The possible explanation for this is that an abnormal CPR probably reflects an established hypoxaemic state and is probably not a predictive parameter, as we were trying to establish in this study. The patients we investigated were stable/mild placental-mediated conditions, i.e. uncompensated IUGR (non-hypoxaemic, non-acidotic) and well-controlled pre-eclamptics (stable control on a single agent).

The clinical phenotypes of IUGR and PE depend on the degree of placental maladaptation and degree of lack of vascular remodelling. Both conditions can be grouped as ischaemic placental disease or placental-mediated disease. In EO-PE there is down-regulation of the interstitial trophoblastic invasion, while endovascular trophoblastic invasion is limited to the decidua. The combined IUGR and PE clinical phenotypes are the result of a more advanced degree of placental maladaptation,[9] and the high number of adverse outcomes in the PE–IUGR group is consistent with this pathophysiology. This is therefore a dynamic process and, depending on the clinical phenotype and placental lesion, will in worse outcomes, result in hypoxia, oligohydramnios (due to decreased foetal perfusion), maternal multi-systemic organ affectation (such as HELLP or eclampsia), foetal acidosis and death.

From whatever clinical phenotype is realised, the path to deterioration can be foetal and/or maternal, depending on levels of placental ischaemia and the associated production of increased levels of toxic factors such as sFLt-1 and endoglin. Present standard monitoring models, done in the early third trimester, may not be predictive of later adverse outcomes. For example, UA RI becomes abnormal only if more than 30 to 40% of the placenta is non-functional,[28,29] MCA RI becomes abnormal only at the onset of hypoxia,[29] and DV changes are late changes in the cascade of cardiovascular deterioration, already reflecting acidosis and myocardial necrosis.[30] Furthermore, the vast majority (> 72%) of 'unexplained' stillbirths at term are so-called appropriate for gestational age, that is between p10 and p50, so biometry is also not entirely helpful.[31]

As early hypoxia and increasing afterload both impact on cardiac function, the MPI is well placed to become a predictor of adverse obstetric outcome, as demonstrated in this study. The use of MPI together with biochemical markers, such as sFlt-1 and PLGF,[32] may further improve its sensitivity. This project is a continuation of our group's quest to further define the clinical use of MPI in high-risk obstetric conditions and find its appropriate place in antenatal foetal surveillance, in the context of present standard foetal monitoring models.

The main limitation of the study is the limited numbers in the groups under investigation, but the results nonetheless highlight the great potential of cardiac Doppler as an important adjunct to standard monitoring models in placental-mediated disease. It makes the case to further corroborate these findings in larger trials and to fine-tune the place and implementation of cardiac Doppler in mainstream monitoring of cases with placental-mediated disease. Another limitation is that it requires training and experience to obtain a reliable MPI result and it can be confounded by user bias. However this parameter shows good reproducibility when the valve-click method of establishing landmarks is used, as we have demonstrated in our study, establishing reference intervals of the MPI in normal pregnancies.[4]

Conclusion

A single elevated value of the MPI (z-score > 4.5) in the third trimester in stable placental-mediated disease is a strong indicator of adverse obstetric outcome later in pregnancy. This has the potential to be incorporated, in conjunction with standard monitoring models, in stable placental-mediated disease to predict an adverse event later in pregnancy and thus to reduce perinatal morbidity and mortality.

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