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# Contribution of the myocardial performance index and aortic isthmus blood flow index to predicting mortality in preterm growth-restricted fetuses

E. HERNANDEZ-ANDRADE*, F. CRISPI*, J. A. BENAVIDES-SERRALDE*, W. PLASENCIA†, H. F. DIESEL‡, E. EIXARCH*, R. ACOSTA-ROJAS*, F. FIGUERAS*, K. NICOLAIDES† and E. GRATACÓS*

**Maternal-Fetal Medicine Department, Institut Clinic de Ginecologia, Obstetricia i Neonatologia (ICGON), Hospital Clinic - Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona and Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Barcelona, Spain, †Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK and ‡Fetal Medicine Unit, Department of Obstetrics, Gynecology and Reproductive Medicine, Universidad Los Andes, Santiago, Chile*

**KEYWORDS:** aortic isthmus; ductus venosus; Doppler; heart; IUGR; mortality; myocardial performance index

## ABSTRACT

***Objectives*** *To evaluate the predictive value for perinatal death of the myocardial performance index (MPI) and aortic isthmus flow index (IFI), as isolated parameters and in a combined model including currently used Doppler indices, in preterm growth restricted (IUGR) fetuses.*

***Methods*** *Umbilical artery, fetal middle cerebral artery (MCA) and ductus venosus (DV) pulsatility indices (PIs) were recorded, along with IFI and MPI, in a cohort of 97 preterm (delivered at between 24 and 34 weeks) IUGR fetuses. Logistic regression analysis was performed to identify those variables that were independently associated with perinatal mortality, and an algorithm to estimate probability of death was constructed including the best combination of parameters.*

***Results*** *With the exception of MCA, all Doppler indices were significantly associated with perinatal death as isolated parameters, but only DV-PI and MPI were found to be independent predictors on multivariate analysis. An algorithm combining DV atrial flow (positive or absent/reversed) and MPI (normal or above 95$^{th}$ percentile) had a better predictive accuracy than did any single parameter. The risk for death in IUGR fetuses below 28 weeks' gestation with present atrial flow in the DV and normal MPI was 18%, with either characteristic abnormal it was 70–73%, and with both abnormal it was 97%. The risk for death in IUGR fetuses above 28 weeks with present atrial flow in the DV and normal MPI was 0.1%, with either abnormal it was 6–7%, and with both abnormal it was 45%.*

***Conclusions*** *MPI is an independent predictor of perinatal death in preterm IUGR fetuses with accuracy similar to that of DV flow. A combination of DV flow with MPI may better stratify the estimated probability of death. IFI does not add to the prediction of perinatal death when used in combination with DV flow. Copyright © 2009 ISUOG. Published by John Wiley & Sons, Ltd.*

## INTRODUCTION

Prediction of perinatal mortality is critical for the clinical management of preterm intrauterine growth restricted (IUGR) fetuses. While gestational age is a major predictor of neonatal outcome[1,2], it needs to be combined with additional parameters in order to weight the risks of prematurity vs. stillbirth. Several approaches have been proposed to monitor these fetuses including arterial and venous Doppler[1–4], cardiotocography (CTG)[5,6] and the biophysical profile score (BPP)[5–7], but to date no management standard for these cases has been established[8–10]. Longitudinal studies have documented that ductus venosus (DV) flow deteriorates earlier than does BPP and could be a more sensitive parameter for the prediction of perinatal mortality in IUGR cases[11,12]. In a recent large multicenter study[1], abnormal DV flow emerged as the strongest predictor for poor perinatal

*Correspondence to:* Dr E. Gratacós, Maternal-Fetal Medicine Department, Hospital Clìnic, Universidad de Barcelona, Sabino de Arana 1, Edificio Helios 208028, Barcelona, Spain (e-mail: GRATACOS@clinic.ub.es)

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outcome. However, its sensitivity for fetal and neonatal death is still only 40–70%[1–3].

In recent years new cardiovascular parameters have been proposed for fetal assessment. Several experimental and clinical studies have demonstrated the association of abnormal aortic isthmus (AoI) flow pattern with adverse outcome[13,14] and later neonatal neurodevelopmental status[15,16] in IUGR fetuses. Additionally, the myocardial performance index (MPI), a Doppler index of combined systolic and diastolic function, has been shown to be increased in IUGR fetuses[17–19], with a linear correlation with the hemodynamic severity stage[20,21]. However, no attempt has been made to estimate the potential contribution of these parameters alone or in combination with other Doppler indices as predictors of perinatal mortality.

This study evaluated the predictive value for perinatal death of the AoI flow pattern and MPI, as isolated parameters and in a combined model including currently used Doppler indices in preterm IUGR fetuses. Secondarily, we explored the best combination of several currently available cardiovascular indices for the prediction of perinatal mortality and the performance of a clinical-decision algorithm including the previously selected parameters.

## METHODS

Singleton pregnancies with IUGR fetuses were prospectively selected from women attending the Maternal–Fetal Medicine Department at Hospital Clínic (Barcelona) and at the Harris Birthright Research Centre for Fetal Medicine (London) from January 2006 to May 2008. The study protocol was approved by the ethics committee at each participating institution, and patients provided their written informed consent. Thirty-seven cases reported here have been included as part of a previous study on IUGR[21]. IUGR was defined as an estimated fetal weight below the 10$^{th}$ centile according to local reference curves[22,23] together with a Doppler pulsatility index (PI) in the umbilical artery (UA) above the 95$^{th}$ percentile[24]. For the purposes of this study only those IUGR fetuses that died or were delivered at between 24 and 34 weeks' gestation were included. Exclusion criteria for the final analysis were birth weight > 10$^{th}$ centile, evidence of fetal infection or structural/chromosomal abnormalities.

Ultrasound assessment was performed using a Siemens Sonoline Antares (Siemens Medical Systems, Erlangen, Germany) or a Voluson 730 Expert (GE Medical Systems, Milwaukee, WI, USA) ultrasound machine with a 6–4 or 6–2-MHz curved array probe. Routine ultrasound examination included a complete morphological examination and fetal weight and amniotic fluid index calculations.

All Doppler measurements were performed in the absence of fetal body movements and, if required, with maternal voluntary suspended respiration. The angle of insonation was kept below 30° and the wall filter set to 70 Hz to avoid sound artifacts. The mechanical and thermal indices were maintained below 1. Because of their correlation with gestational age, all individual Doppler data were normalized by converting the measurements into *Z*-scores (standard deviations from the mean for gestational age)[24–28]. UA-PI and end-diastolic flow (EDF) characteristics were obtained from a free loop of the umbilical cord. UA flow was divided into three categories according to the EDF characteristics as: present, absent and reversed. Fetal middle cerebral artery (MCA)-PI was measured in a transverse view of the fetal skull at the level of its origin from the circle of Willis. DV-PI and flow during atrial systole were obtained from a mid-sagittal or transverse section of the fetal abdomen[25]. DV flow was divided into three categories according to the PI and atrial flow as: normal (PI below the 95$^{th}$ percentile); increased pulsatility (PI at or above the 95$^{th}$ percentile); and absent/reversed atrial flow (RAV). AoI blood flow velocity index (IFI) was obtained either in a sagittal view of the fetal thorax with clear visualization of the aortic arch, placing the Doppler sample volume between the origin of the left subclavian artery and the confluence of the ductus arteriosus[26], or in a cross-sectional view of the fetal thorax at the level of the three vessels and trachea view, placing the Doppler gate in the aorta just before the convergence of the arterial duct[27]. IFI was calculated as: (systolic + diastolic)/systolic velocity integrals[26]. Left MPI was obtained in a cross-sectional image of the fetal thorax and an apical four-chamber view, placing the Doppler sample volume on the medial wall of the ascending aorta including the aortic and mitral valves as previously described[29]. The movements (clicks) of the valves in the Doppler tracing were used as landmarks to calculate the isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT), and the ejection time (ET). MPI was calculated as (ICT + IRT)/ET, and was dichotomized into two categories as: normal (MPI below the 95$^{th}$ percentile) and abnormal (MPI at or above the 95$^{th}$ percentile)[28]. For analysis only Doppler estimations recorded within the last 72 h before delivery or fetal demise were included.

The indications for delivery included deterioration of fetal venous indices (absent or reversal of atrial flow in the DV), decelerative CTG, persistent abnormal BPP and maternal complications secondary to pre-eclampsia. When, according to these criteria, elective delivery was indicated for fetuses at a gestational age below 26 weeks, the option of expectant management was discussed with parents and accepted if requested. The managing clinicians were blinded to the results of IFI and MPI. At delivery, gestational age, birth weight, Apgar scores and umbilical pH were recorded.

### Statistical analysis

Variables were log- or square-transformed to achieve normal distribution. The diagnostic performance for perinatal mortality was evaluated by means of $2 \times 2$ tables where standard cut-offs for predictive variables were used.

Logistic regression analysis was used to explore the association of UA-, MCA- and DV-PI, and IFI and MPI (as continuous variables) with perinatal mortality, defined

as either intrauterine death or neonatal death within the first 28 days of postnatal life. Assumptions for logistic regression were checked by assessing the log-distribution of the residuals.

Additionally, a stepwise variable selection procedure was performed in which all predictive variables were introduced as categorical parameters (normal/abnormal). Standard rules were used for variable selection in the stepwise procedure[30]. Gestational age at ultrasound examination was also included in the final model, as it has been shown to be one of the strongest predictors for perinatal mortality in IUGR fetuses[1]. For each predictor, the cut-off best associated with perinatal mortality on univariate analysis was used. The model coefficients were used to predict the mortality risk for each combination of the significant predictive variables, resulting in a risk score. From the final model, risks were stratified for each combination of predictive variables for fetuses that were delivered before and after 28 weeks' gestation.

Data were analyzed using the SPSS 13.0 statistical package (SPSS, Chicago, IL, USA). Differences were considered significant when $P$ was $< 0.05$.

## RESULTS

Maternal characteristics, Doppler indices and perinatal outcome of the study population are shown in Tables 1 and 2. A total of 97 preterm IUGR cases were included, 82 cases from the Maternal–Fetal Medicine Department at Hospital Clínic and 15 from the Harris Birthright Research Centre for Fetal Medicine. The median gestational age at delivery was 30 weeks and the median birth weight was 956 g. The indications for delivery were deterioration of fetal venous indices (49 cases), decelerative CTG (12 cases), persistent abnormal BPP (5 cases), maternal complications secondary to pre-eclampsia (23 cases) and fetal death (8 cases). The overall perinatal mortality was 22.7%, including eight intrauterine and 14 neonatal deaths. Postnatal deaths occurred at between 1 and 28 days following delivery and the causes of death were severe respiratory distress, massive brain hemorrhage and sepsis. All cases other than the eight intrauterine deaths were delivered by Cesarean section. Those IUGR fetuses that died pre- or postnatally were delivered earlier and had lower birth weight as compared with survivors. All Doppler indices with the exception of MCA were significantly different in cases that died as compared with survivors.

Univariate analysis demonstrated that all Doppler indices (DV-PI, $P < 0.0001$; UA-PI, $P < 0.0001$; MPI, $P < 0.0001$; IFI, $P < 0.0001$) with the exception of MCA-PI ($P = 0.068$) were significantly associated with perinatal mortality. Multivariate analysis identified UA-PI (estimated odds ratio, 3.01; $P = 0.02$), DV-PI (estimated odds ratio, 3.69; $P = 0.008$) and MPI (estimated odds ratio, 1.39; $P = 0.02$) as statistically significant independent predictors for perinatal mortality (Table 3). IFI did not show any significant contribution to the explanation of perinatal mortality. The Hosmer–Lemeshow statistic was calculated as a measure of goodness-of-fit ($\chi^2 = 9.292$, $P = 0.318$).

When gestational age was included in the model and variables were dichotomized to normal/abnormal, only gestational age (below 28 weeks), DV atrial flow (RAV) and MPI (abnormal) significantly and independently accounted for perinatal mortality ($R^2$ Nagelkerke, 50%) (Table 4). The Hosmer–Lemeshow statistic was performed as a measure of goodness-of-fit ($\chi^2 = 2.135$, $P = 0.545$). Table 5 shows the diagnostic performance of different standard cut-offs of the predictive variables for perinatal mortality. According to this model, risk was stratified for each combination of predictive variables (Figure 1) and a simplified score was modeled (Table 6).

**Table 1** Maternal characteristics and perinatal outcomes of the study population ($n = 97$)

| *Parameter* | *Median (IQR) or % (n)* |
|---|---|
| Maternal characteristics | |
| Maternal age (years) ($n = 92$) | 31 (28 to 36) |
| Caucasian | 70.7 (65/92) |
| Smoker | 17.0 (15/88) |
| Primiparous | 58.3 (56/96) |
| Pre-eclampsia | 58.8 (57/97) |
| Doppler recordings ($n = 97$) | |
| UA-PI | 12 (5 to 15) |
| MCA-PI | −2 (−3 to −2) |
| DV-PI | 3 (1 to 5) |
| IFI | −3 (0 to −5) |
| MPI | 3 (0 to 4) |
| Delivery data | |
| Gestational age at delivery (weeks) ($n = 97$) | 30 (28 to 32) |
| Birth weight (g) ($n = 95$) | 956 (694 to 1170) |
| Birth weight percentile ($n = 95$) | 1 (0 to 1) |
| 5-min Apgar score < 7 | 15.1 (13/86) |
| Umbilical artery pH < 7.20 | 38.4 (33/86) |
| Perinatal outcome | |
| Days in neonatal intensive care unit ($n = 86$) | 32 (14 to 50) |
| Perinatal death | 22.7 (22/97) |
| Bronchopulmonary dysplasia | 8.0 (7/87) |
| Intraventricular hemorrhage III–IV | 6.3 (5/80) |
| Necrotizing enterocolitis | 3.4 (3/87) |
| Adverse outcome | 29.9 (29/97) |

Doppler values are expressed in *Z*-scores. Adverse outcome was defined by the presence of perinatal death, bronchopulmonary dysplasia, neonatal intraventricular hemorrhage Grade III or IV or necrotizing enterocolitis. DV, ductus venosus; IFI, aortic isthmus flow index; IQR, interquartile range; MCA, middle cerebral artery; MPI, myocardial performance index; PI, pulsatility index; UA, umbilical artery.

## DISCUSSION

This study evaluated the independent and combined contribution to the prediction of mortality of cardiovascular parameters. The findings confirmed that DV flow is the strongest Doppler predictor for perinatal mortality in preterm IUGR[1,2]. However, MPI showed an independent association with perinatal death, with a predictive accuracy similar to that of DV-RAV. The data suggest that

**Table 2** Doppler indices and antenatal surveillance in intrauterine growth restricted fetuses

| *Variable* | *Survivors* (n = *75)* | *Perinatal deaths* (n = *22)* |
|---|---|---|
| Doppler index | | |
| UA-PI | 6.3 (4 to 10) | 17.1 (13 to 88)* |
| MCA-PI | −2.5 (−3 to −2) | −1.9 (−2 to 0.3) |
| DV-PI | 1.4 (0 to 3) | 6.7 (4 to 10)* |
| IFI | −1 (−6 to 4) | −6 (−9 to 5)* |
| MPI | 1.9 (0 to 4) | 3.3 (1 to 4)* |
| Delivery data | | |
| Gestational age at delivery (weeks) | 31 (29 to 32) | 27 (26 to 28)* |
| Birth weight (g) | 1045 (794 to 1252) | 539 (400 to 590) ($n = 20$)* |
| Birth weight percentile | 0 (0 to 1) | 0 (0 to 1) ($n = 20$) |
| 5-min Apgar < 7 | 8.2 (6/73) | 61.5 (8/13)* |
| Umbilical artery pH < 7.20 | 31.1 (23/74) | 83.3 (10/12) |
| Neonatal outcome | | |
| Bronchopulmonary dysplasia | 4.0 (3/75) | 33.3 (4/12)* |
| Intraventricular hemorrhage III–IV | 5.9 (4/68) | 8.3 (1/12)* |
| Necrotizing enterocolitis | 4.0 (3/75) | 0 (0/12) |

Data are shown as median (interquartile range) or % ($n$), with Doppler values in $Z$-scores. *$P < 0.05$ compared to survivors. DV, ductus venosus; IFI, aortic isthmus flow index; MCA, middle cerebral artery; MPI, myocardial performance index; PI, pulsatility index; UA, umbilical artery.

**Table 3** Estimated odds ratios (OR) for perinatal mortality by logistic regression (multivariate analysis)

| *Variable* | *Estimated OR (95% CI)* | P |
|---|---|---|
| UA-PI | 3.012 (1.187–7.644) | 0.02 |
| MCA-PI | — | 0.072 |
| DV-PI | 3.690 (1.412–9.642) | 0.008 |
| IFI | — | 0.178 |
| MPI | 1.386 (1.052–1.825) | 0.02 |

Estimated ORs represent the increase in likelihood for each increased unit of standard deviation. DV, ductus venosus; IFI, aortic isthmus flow index; MCA, middle cerebral artery; MPI, myocardial performance index; PI, pulsatility index; UA, umbilical artery.

**Table 4** Estimated odds ratios (OR) for perinatal mortality by logistic regression analysis after dichotomization of variables and inclusion of gestational age into the model

| *Variable* | *Estimated OR (95% CI)* | P |
|---|---|---|
| GA < 28 weeks | 34.608 (6.579–182.045) | < 0.001 |
| DV-RAV | 12.241 (1.938–77.307) | 0.008 |
| MPI > 95$^{th}$ centile | 10.423 (1.005–109.332) | 0.049 |

Estimated ORs represent the increase in likelihood for each increased unit of standard deviation. DV-RAV, ductus venosus reversed/absent atrial flow; GA, gestational age; MPI, myocardial performance index.

a score combining DV-RAV and MPI might improve the predictive accuracy obtained with each parameter alone. These findings support the notion that a combination of several cardiovascular indices may improve clinical management by better stratifying the estimated probability of death.

With the exception of MCA, all the Doppler indices evaluated in this study showed a significant association with perinatal mortality as isolated parameters. However, only UA- and DV-PI and MPI remained as independent predictors of mortality in a multivariate analysis. When variables were categorized to explore their predictive value in clinical practice, only DV-RAV and abnormal MPI showed an independent association with perinatal mortality, which persisted after adjusting for gestational age, so they could be used to construct a clinical-decision algorithm. Our results are in line with previous studies integrating several Doppler indices and showing DV flow as the best predictor for perinatal death in preterm IUGR[1–3]. The data are also in agreement with previous studies on UA and MCA, where a lack of improvement in the prediction of mortality after adjustment for other Doppler parameters and gestational age has been shown[1,2,31,32]. Finally, as previously reported[1–3], gestational age at delivery was so strongly associated with perinatal outcome that the algorithm derived had to incorporate this variable in order to obtain meaningful results.

This study first reports that MPI is independently associated with perinatal mortality, and that its combination with DV flow characteristics could improve the predictive value of current fetal Doppler evaluation. MPI is a global cardiac parameter that evaluates both systolic and diastolic function by including the measurement of isovolumetric and ejection times[33]. Use of the Doppler clicks of opening and closure of the mitral and aortic valves to estimate the time-periods for MPI calculation enhances the reproducibility of the measurement[29]. In a recent study we showed that MPI correlates with the clinical hemodynamic deterioration of IUGR fetuses and with progressively increased levels of cardiac dysfunction biomarkers such as B-type natriuretic peptide[21].

The evaluation of IFI as an isolated parameter in this study was consistent with previous series reporting that IUGR cases with AoI reversed diastolic flow have

 

**Table 5** Predictive values for perinatal mortality of significant parameters in the logistic regression model following dichotomization of variables

| *Variable* | *Detection rate (% (95% CI))* | *False-positive rate (% (95% CI))* | *Positive likelihood ratio (95% CI)* | *Negative likelihood ratio (95% CI)* |
|---|---|---|---|---|
| Gestational age < 28 weeks | 87 (55–92) | 11 (2–15) | 7.91 (5–15) | 0.14 (0.08–0.8) |
| DV-RAV | 57 (32–76) | 5 (2–13) | 11.40 (7–15) | 0.45 (0.2–1.4) |
| MPI > 95$^{th}$ centile | 95 (77–99) | 52 (43–66) | 1.82 (1.3–2.3) | 0.10 (0.01–0.7) |

DV-RAV, ductus venosus reversed/absent atrial flow; MPI, myocardial performance index.

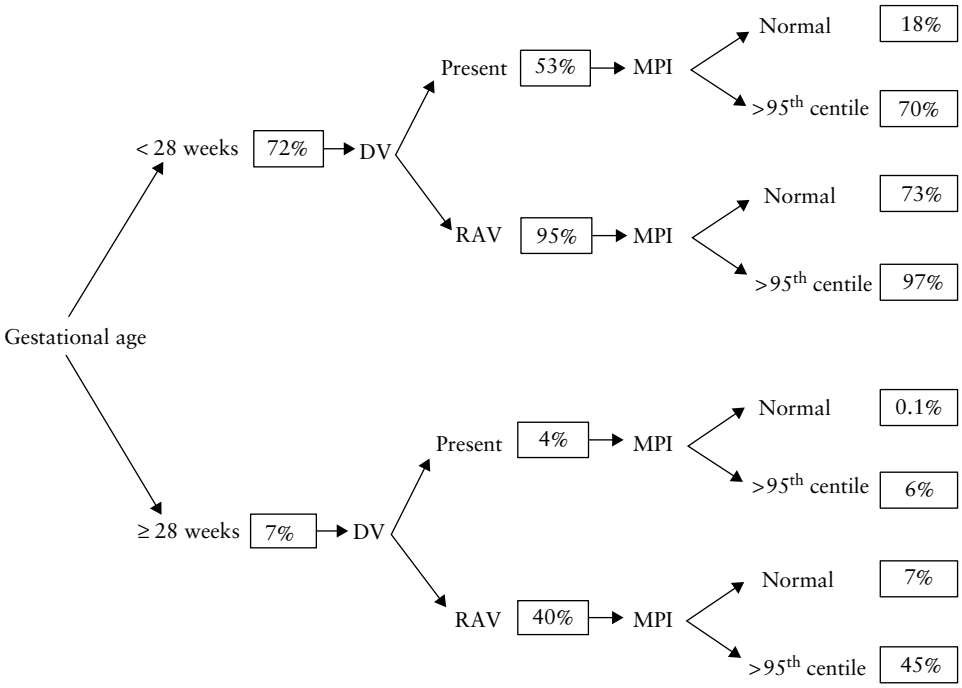


**Figure 1** Flow chart for estimation of probability (as a percentage) of perinatal death according to gestational age at ultrasound, ductus venosus flow (DV) and myocardial performance index (MPI). RAV, reversed/absent atrial flow.

**Table 6** Performance of a cardiovascular risk score including DV flow characteristics and MPI for the prediction of perinatal mortality

| *Cardiovascular risk score* | *Estimated probability of perinatal death (%)* |
|---|---|
| Gestational age < 28 weeks | |
| 0 | 18 |
| 1 | 70–73 |
| 2 | 97 |
| Gestational age ≥ 28 weeks | |
| 0 | 0.1 |
| 1 | 6–7 |
| 2 | 45 |

Cardiovascular risk score was defined as: 0, present atrial flow in ductus venosus (DV) together with normal values of myocardial performance index (MPI) (< 95$^{th}$ percentile); 1, DV reversed/absent atrial flow (RAV) or MPI ≥ 95$^{th}$ centile; 2, DV-RAV and abnormal MPI.

a deterioration of cardiac function[34] and a poorer perinatal outcome[13,14]. However, multivariate analysis demonstrated that IFI does not add to DV-PI in the prediction of mortality. These findings seem to be explained by an intrinsic correlation of AoI IFI with DV-PI and other cardiovascular parameters[34–36]. Furthermore, in a longitudinal analysis of the evolution of the AoI and other Doppler indices in preterm IUGR, we demonstrated that the IFI becomes abnormal earlier than does DV flow[37] in the sequence of fetal hypoxic deterioration. This may also partially explain a lower predictive capacity of IFI as an acute marker for a late event such as mortality. It must be noted that our findings do not preclude the strong predictive value of IFI when used as an isolated parameter[13–15]. On the other hand, this study focused on perinatal death, but not on neurological outcome. IFI has been reported to constitute a strong predictor of morbidity, mainly long-term adverse neurodevelopmental outcome[15,16], an aspect not evaluated in this study.

This study has several limitations. The managing clinicians were not blinded to UA, MCA and DV results. Indeed, DV-RAV was a delivery criterion and therefore we acknowledge that this may have distorted the expected perinatal outcome. However, this limitation is also present

 

in many studies evaluating fetal/neonatal mortality[1–3]. On the other hand, the study evaluated the predictive value of Doppler indices, but the data were not combined with other proposed means for fetal monitoring of preterm IUGR, such as BPP and computerized CTG[4–7,38], and this may limit applicability of these findings in certain clinical settings.

In conclusion, this study suggests that a combination of MPI with DV flow characteristics improves the predictive value of these parameters alone. The results support the notion that combined cardiovascular scores might refine considerably the prediction of perinatal mortality at different gestational ages at delivery in preterm IUGR cases. Gestational age at ultrasound examination was again found to be the strongest predictor of mortality, and it should be considered when any scoring system for the prediction of perinatal mortality is being developed. Larger prospective studies are required to further confirm our results and to evaluate the potential clinical value of MPI. Additionally, its correlation and potential interaction with other clinical parameters such as BPP and computerized CTG remain to be assessed.

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