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Research Article

Application of Cardiovascular Profile Score and Myocardial Performance Index to Predict Perinatal Mortality in Fetus with Intrauterine Growth Restriction Followed Up in a University Hospital in Brazil during 2022

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Abstract

Objective: To assess whether fetal cardiovascular score and myocardial performance index (MPI) are associated with worse neonatal outcomes in fetuses diagnosed with intrauterine growth restriction (IUGR) followed at the Clinics Hospital of UFMG in 2022.

Methodology: This is a prospective and longitudinal study that included patients followed at the high-risk prenatal care at the Clinics Hospital of UFMG for IUGR. The fetuses were monitored with Doppler velocimetry, and the timing of delivery was guided according to institutional protocol. Fetal cardiac function was evaluated using the fetal cardiovascular score and MPI, and perinatal outcomes were assessed. Statistical association tests included calculation of odds ratio (OR), Fisher's exact test, Student's t, and Pearson's correlation test.

Results: It was identified associations between an increased risk of death for cases where there were alterations in the percentile of umbilical artery doppler, fetal cardiovascular score, and ductus venosus. Associations were also observed between the outcome of death and lower mean CPR percentiles, lower ICT values, lower gestational ages at birth, as well as associations with higher mean percentiles of uterine artery Doppler and TE values. An association was also identified between neonatal death and alteration of MPI parameters, as well as the correlation of this and lower Apgar scores at 5 minutes.

Conclusion: The parameters of fetal cardiovascular score and myocardial performance index, as well as alterations in fetal Doppler velocimetry, are associated with worse neonatal outcomes.

Keywords: *Intrauterine Growth Restriction; Fetal Echocardiography; Fetal Doppler Velocimetry; Huhta's Cardiovascular Score; Myocardial Performance Index*

Introduction

Intrauterine growth restriction (IUGR) has a significant impact on perinatal mortality. It is estimated to affect between 5 - 10% of all pregnancies and may result from a variety of maternal and fetal conditions, such as placental insufficiency [1-2,4]. Doppler velocimetry is a widely used tool for monitoring and predicting the severity of growth restriction, playing a fundamental role in determining the ideal time for birth, considering the risks associated with prematurity.

The classification of intrauterine growth restriction (IUGR) was refined through the Delphi consensus [5,6] resulting in the distinction of two different groups. Early IUGR refer to those cases diagnosed before 32 weeks of gestation, while late IURG cases are identified after 32 weeks. Both subtypes present distinctions regarding clinical manifestations, their association with hypertensive disorders, characteristics of Doppler study, as well as patterns of deterioration and the severity of placental dysfunction. These factors impact the adaptive mechanisms and, consequently, the way cardiac dysfunction occurs between the groups [5,6].

Table 1 highlights the conceptual differences between small-for-gestational-age fetuses and intrauterine growth restriction, distinguishing between early and late cases [4,7].

Type	Concept
Small for gestational age	Fetal weight between the 3rd and 10th percentiles, with maternal and fetal doppler flowmetry showing no changes.
Restricted intrauterine growth	Fetal weigh PEF below the 3rd percentile, or between the 3rd and 10th percentiles, with doppler flowmetry changes.
Early (< 32 weeks)	Fetal weigh or abdominal circumference below the 3rd percentile Or doppler flowmetry of the umbilical artery with absent diastole Or fetal weigh or abdominal circumference below the 10th percentile, associated with either doppler velocimetry of the umbilical artery with PI above the 95th percentile, or doppler flowmetry of the uterine arteries with mean PI above the 95th percentile.
Late	Fetal weigh below the 3rd percentile. Or 2 two of the criteria: - Abdominal circumference below the 10th percentile; - Drop of more than 2 quartiles in fetal weigh and abdominal circumference; - Doppler velocimetry of the umbilical artery with PI above the 95th percentile; - CPR below the 5th percentile.

Table 1: *Differentiation between fetuses that are small for gestational age and early and late intrauterine growth restriction [4].*

Placental insufficiency and hypoxia predominantly trigger hemodynamic changes in the peripheral vascular territory, aiming to increase blood supply to vital organs, such as the brain, myocardium and adrenal glands. These hemodynamic adaptations are probably linked to the influence of oxygen and carbon dioxide pressures on certain chemoreceptors. This phenomenon, which seeks to ensure an effective redistribution of blood flow, prioritizing essential organs to maintain vital functions in the face of challenging conditions imposed by placental insufficiency and hypoxia [1,7,8], can result in the interruption of cardiomyocyte growth, generating cardiac changes structural and functional. To evaluate this function, two methods used and applied in the echocardiographic evaluation of fetuses with congenital heart diseases are the fetal cardiovascular score and the myocardial performance index.

The cardiovascular profile score is a scoring system created with the aim of determining the prognosis in fetuses with congenital heart disease and/or heart failure. To assess cardiac function, the parameters hydrops, cardiomegaly, arterial and venous Doppler and cardiac function are considered, totaling five parameters. Each one receives values from zero to two points according to the absence or presence of dysfunction [9]. In the presence of the disfunction, the score must be subtracted. A score ≤ 7 has prognostic power in predicting adverse neonatal outcomes, already correlated with biochemical markers of cardiac dysfunction in fetuses with IUGR [8].

Category	0	1	2
Hidropsy	None	Ascites, pleural effusion ou pericadial effusion	Skin edema
Cardiac area	≥ 0,20 or ≤ 0,35	0,35-0,50	>0,50 or < 0,20
Heart function	Normal TV and MV RVILV S.F. > 0.28 Biphasic filling	Holosystolic TR or RV/LV S.F. < 0.28	Holosystolic MR or TR dP/dt < 400 or Monophasic filling
Venous Doppler venoso	Absence of atrial pulsation in the umbilical vein and normal venous duct	Absence of atrial pulsation in the umbilical vein and negative A wave in the venous duct	Atrial pulsation in the umbilical vein
Arterial Doppler	Umbilical artery full diastole	Umbilical artery full diastole	Reverse diastole in the umbilical artery

Table 2: *Cardiovascular profile score [9].*

AEDV: Absent End Diastolic Velocity; dP/dt: Change in Pressure Over Time of TR Jet; DV: Ductus Venosus; LV: Left Ventricle; MR: mitral Valve Regurgitation; MV: Mitral Valve; SF: Ventricular Shortening Fraction; TR: Tricuspid Valve Regurgitation; TV: Tricuspid Valve; REDV: Reversed End Diastolic Velocity; RV: Right Ventricle; UV: Umbilical Vein.

The myocardial performance index (MPI) was introduced in 1995 by Tei and his collaborators as a potential predictor of global cardiac function [10-12]. It consists of the sum of the isovolumetric relaxation time and the isovolumetric contraction time, divided by the left ventricular ejection time [9,10,12]. MPI can be calculated by estimating the total isovolumic time (TI) over the TE (ejection time) or by estimating the individual isovolumic contraction (ICT) and relaxation (IRT) times over the TE. ICT begins when the atrioventricular valves close and ends when the semilunar valves open. TE is the period between the opening and closing of the semilunar valves. The IRT is the period from the closure of the semilunar valves to the opening of the atrioventricular valves [3,9,12]. The measurement can be performed from a "5-chamber" view, using the spectral doppler technique, by positioning the pulsed wave detection gate with a size of 2 to 3 mm at the level of the junction of the mitral and aortic valve rings, that exhibit anatomical contiguity. All measurements to calculate MPI need to be obtained in the same cardiac cycle [7]. It is worth mentioning that IPM is a non-invasive method that uses time intervals in its performance, presents small inter- and intra-observer variability, and is not influenced by ventricular geometry and heart rate. A significantly higher MPI is expected in fetuses with IUGR compared to fetuses with adequate growth. Elevated MPI is observed in the early stages of cardiac adaptation, presumably secondary to hypoxia, and remains elevated throughout the different stages of deterioration, in the same way as PI of the ductus venosus and PI of the isthmus of the aorta. Available evidence from longitudinal studies has demonstrated that an abnormal increase in MPI can be detected before umbilical artery Doppler becomes abnormal and shows absent or reversed end-diastolic blood flow [13,14].

The finding of a higher MPI appears as a possible discriminator between IUGR and small for gestational age fetuses in fetuses with reduced biometry but with normal doppler. However, although there is still no evidence-based strategy that includes it among the parameters for monitoring fetuses with IUGR, it is already recognized that MPI represents a direct indicator of cardiac dysfunction [7,13,14]. The combination of MPI with doppler and cardiovascular profile score demonstrates potential for contributing to antenatal monitoring strategies, predicting neonatal morbidity and mortality and, potentially, determining the ideal time for birth [4,6,13,16,18,22].

Objective of the Study

The objective of this work was to evaluate whether the pathological fetal cardiovascular score and the myocardial performance index are associated with neonatal mortality in fetuses diagnosed with restricted intrauterine growth, which were monitored at Clinical Hospital of the Federal University of Minas Gerais during 2022.

Methodology

It was a prospective observational study that analyzed pregnancies referred to Clinical Hospital of the Federal University of Minas Gerais with confirmation of IUGR and small-for-gestational-age fetuses. Patients who agreed to participate in the research signed informed consent form. All patients with gestational age confirmed by ultrasound performed before 20 weeks of gestation were included. The exclusion criteria were malformations of any nature, multiple pregnancies, loss of prenatal care and birth occurred in another hospital.

The patients were referred for fetal echocardiography. All exams were conducted by the same experiment examiner, using the GE®, LOGIQ P9 ultrasound device. The cardiovascular score was determined as described by Hutha., *et al* [9,16]. Likewise, the determination of the MPI followed the guidelines described by TEI and collaborators.

In this sample, the objective is to identify whether fetuses with IUGR, presenting a MPI above 95th percentile and a fetal cardiovascular score less than 7 have a higher risk of mortality.

Statistical analysis was performed using Fisher's exact test, which assesses the homogeneity of risks in two groups. For other quantitative outcomes, the comparison of means was performed using the Student's t test or its non-parametric equivalent, the Mann-Whitney test (Wilcoxon rank sum), if the variable did not present a normal distribution. Determining the ideal time for delivery followed the institutional protocol [4], considering the severity of IUGR and other maternal and fetal criteria that complicate pregnancy. Neonatal outcomes were assessed from medical records. Inferences or statistical association tests were carried out by calculating the Odds Ratio (OR) and confidence interval.

Results

The database consisted of 38 patients. The analysis of the sample composition shows that 26% of the patients were single, and 47% had completed secondary education. The average age of the women was 30 years old, with the age range varying between 14 and 41 years old. In 44% of cases no risk factor was identified, followed by 21,5% of patients that had chronic arterial hypertension. 36% did not use any medication, and 23.7% used antihypertensive drugs. 92.1% of pregnant women denied smoking and 97.1% denied drinking alcohol. All participants denied using illicit drugs. Regarding obstetric history, 36.8% of women were primiparous. Gestational age at assessment ranged from 22 to 38 weeks, with a mean of 32 weeks and standard deviation of 4. The maximum weight percentile, as expected due to the inclusion criteria, was 10. The minimum weight percentile was 1, while the mean and standard deviation were 4 and 3, respectively. Therefore, considering the cutoff point of less than or equal to seven as altered, the pathological cardiovascular profile score was observed in five cases (Table 3). The 95 percentile was the cutoff point for the Myocardial Performance Index. 32 of the 38 patients presented pathological results (Table 4). Data were collected approximately 2 weeks and 4 days before delivery for the group of cases associated with neonatal death, and 3 weeks and 2 days was the median interval for all cases.

Patologic Cardiovascular Profile Score	Frequency	Percentage (valid)
No	33	86,84%
Yes	5	13,16%

Table 3: *Frequency table: Cardiovascular profile score - pathologic.*

Pathologic MPI	Frequency	Percentage (valid)
No	6	15,79%
Yes	32	84,21%

Table 4: *Frequency table: Pathologic MPI*

Myocardial performance index (MPI)

Although there were a small number of deaths, making it unlikely to detect any statistically significant relationship, the fetal cardiovascular score showed a statistically significant association at a confidence level of 0.1%.

		Death			
Independent variable		No	Yes	OR	p-value
Pathologic Cardiovascular Profile Score	No	33	0		
	Yes	2	3	Inf	0,001
Pathologic MPI	No	6	0		
	Yes	29	3	Inf	1,000

Table 5: *Cross table: Death vs independent variables.*

IPM: Myocardial Performance Index.

Neonatal death was associated with independent quantitative variables, such as cardiovascular profile score and ET.

	Mean ± S.D. Independent variable. (n)		
Independent variable	**Death = NO**	**Death = YES**	**p-value**
ICT	52,2 ± 12,6 (n = 35)	42,4 ± 3,1 (n = 3)	0,005
IRT	60,9 ± 18,9 (n = 35)	55,5 ± 11,1 (n = 3)	0,508
ET	158,8 ± 20,7 (n = 35)	173,5 ± 3,9 (n = 3)	0,002
Myocardial Performance Index (MPI)	95,3 ± 12,9 (n = 35)	97,8 ± 1,4 (n = 3)	0,277

Table 6: *Table comparing the means (T-test): Death.*

ICT: Isovolumic Contraction Time; MPI: Myocardial Performance Index; IRT: Isovolumic Relaxation Time; ET: Ejection Time.

Discussion

The cardiovascular system is one of the fetal systems impacted by chronic hypoxia, with implications for the maintenance of intrauterine life, and repercussions on extra-uterine life. The evolution of medical knowledge and ultrasound devices led to the incorporation of echocardiography in fetal assessment, initially only in the morphology and detection of congenital heart diseases and, more currently, in the assessment of functional aspects, further expanding knowledge of the pathophysiology of IUGR.

Firstly, the minimum cardiovascular profile score was 7. It was considered normal in 86.84% of patients. A statistically significant association between pathologic cardiovascular profile score and the risk of death was demonstrated (OR = infinity; CI: 3.7 to infinity). In a study developed by Huhta., *et al*. it was observed that in fetuses with congenital heart disease and a cardiovascular profile score ≤ 7, mortality was significantly higher than fetuses with a final score ≥ 8 (87.5% vs. 15.2%) [17]. The data obtained in our research for this parameter allow us to extrapolate that even for fetuses without congenital heart disease, the heart failure inferred from lower cardiovascular profile scores is associated with mortality.

In another study from Huhta., *et al*. [16] that investigated the applicability of the cardiovascular profile score in predicting perinatal outcomes specifically in cases of IUGR, seventy-five fetuses were monitored with Doppler velocimetry and cardiovascular assessments, and neonatal mortality and cerebral palsy were the primary outcomes. The parameters most associated with predicting worse perinatal outcomes were cardiomegaly, monophasic atrioventricular filling, holosystolic tricuspid regurgitation and disfunction on venous doppler velocimetry. In our study, no fetuses with the parameters hydrops, umbilical vein pulsation and holosystolic regurgitation were identified, although cardiovascular profile score values lower than 7 and the doppler velocimetry of the ductus venosus OR = infinity; CI: 5.5 to infinity) demonstrated an association with the risk of death.

Regarding the MPI, 84.21% of patients presented altered results, with very close medians and means, reinforcing the validity of the test. An association was observed between mortality and lower ICT values (mean difference = -9.8 ICT; CI: -3.7 to -15.8) and higher TE values (mean difference = 14.5 TE; CI: 5.9 to 23.4). No relationship between mortality and changes in IRT values was observed. The data from our research differ from those from a study carried out by Öcal., *et al*. [18]. It was a cross-sectional case-control type, which evaluated the applicability of the MPI in the assessment of IUGR. 40 women with fetuses with IUGR and 40 women with normal weight fetuses, between 29 and 39 weeks of gestation, were evaluated. In the group of fetuses with IUGR, the mean IRT was significantly lower and there were no statistically significant differences between the groups in IPM, ICT and ET. However, when evaluating the research population, we observed some differences, especially in relation to age, with our research group being slightly older, with an average of 30 years old, and an age range varying between 14 and 41 years old, while in the research by Öcal., *et al*. [18], the groups had an average age of 26 years. Furthermore, in our research, 66% of patients had some risk factor for IUGR, with chronic arterial hypertension being present in 21.5% of participants. In the mentioned study, patients with any comorbidities were excluded.

We understand that the results of this study do not have immediate practical implications for clinical practice. Although the sample of this study is representative of the profile of patients treated at the Clinical Hospital of the Federal University of Minas Gerais, it is a small sample and is largely composed of pregnant women with pre-existing health conditions, who use medications, or who impose a view on this study. Furthermore, reinforcing the small sample, it was not possible to stratify the groups by gestational age to reinforce the distinction of the impact of prematurity on mortality, and it was also not possible to separate the groups between those with present and absent diastole in the umbilical artery and changes in MPI. Additional studies with larger samples are necessary to continue the investigations. Expanding the sample, including extending the research to other centers, is essential to ensure a more robust and representative analysis, allowing for more effective control of views. One of the objectives of expanding the sample should include stratifying IUGR cases by

gestational age, to help delimit the impact of prematurity on morbidity and mortality. Expanding the sample will allow control of variables such as maternal age, pre-existing health conditions or use of medications that may influence the severity of growth restriction, or even the severity of fetal cardiac dysfunction, with longitudinal monitoring of newborns to assess the effects of IUGR on child health, such as neurocognitive and cardiovascular development in the long term.

Conclusion

Pathologic cardiovascular profile score and myocardial performance index are associated with higher mortality. Prematurity, which is still the main cause of neonatal mortality today, adds to the challenge of the disease, requiring health professionals to make every effort to prevent it.

However, despite these associations, the applicability of the cardiovascular profile score and myocardial performance index in predicting neonatal outcomes in fetuses with restricted intrauterine growth remains uncertain. Additional studies with more extensive samples are necessary to continue the investigations, incorporating other new markers and technologies such as TAPSE, MAPSE and fetal STRAIN, which still have uncertain applicability.

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