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Pulmonary Vein Flow Impedance: An Early Predictor of Cardiac Dysfunction in Intrauterine Growth Restriction

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Keywords
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Abstract
Introduction: In intrauterine growth restriction (IUGR), increased uteroplacental vascular impedance contributes to preferential flow to left ventricle (LV), with consequent alteration of its compliance and increased left atrial (LA) pressure. Pulmonary vein pulsatility index (PVPI) reflects the increased impedance to LA filling and could be used as a cardiac monitoring parameter in IUGR. ***Material and Methods:*** A total of 27 IUGR fetuses (group 1), 28 fetuses with appropriate growth for gestational age from hypertensive mothers (group 2), and 28 controls (group 3) were studied. Pulsatility indices (PIs) of pulmonary veins and ductus venosus were calculated by Doppler echocardiography. Obstetric ultrasound was used to assess the PIs of uterine, umbilical, and middle cerebral arteries. Statistical analysis used analysis of variance, post-hoc Tukey, and Pearson's tests. ***Results:*** Mean PVPI was higher in IUGR group (1.27 ± 0.39) when compared to groups 2 (1.02 ± 0.37; $p = 0.01$) and 3 (0.75 ± 0.12; $p < 0.001$). In group 2, moderate correlation between PVPI and ductus venosus pulsatility index (DVPI) was found but not between PVPI and cerebroplacental ratio (CPR). ***Discussion:*** Higher PVPI in IUGR reflects decreased LV compliance and altered LA dynamics. As LV dysfunction precedes right ventricle, our results suggest that PVPI could be an early echocardiographic parameter of fetal diastolic function in IUGR.

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Introduction

Hypertensive disorders in pregnancy are among the most important causes of maternal and perinatal morbidity and mortality worldwide [1, 2].

Abnormal placental angiogenesis has emerged as one of the main pathophysiological features of placental insufficiency and angiogenic markers, including alpha fetoprotein levels and soluble fms-like tyrosine kinase/placental growth factor ratio are important tools to predict pre-ec-

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lampsia (PE) and intrauterine growth restriction (IUGR) [2, 3]. In an attempt to improve the accuracy of the detection of PE, some publications have shown that the more effective approach is the one that combines maternal risk history with measurements of blood pressure, uterine artery Doppler, and serum biomarkers [4]. Increased pulsatility index (PI) of the uterine and umbilical arteries are considered to be important Doppler ultrasound signs of placental dysfunction and the assessment of fetal-placental hemodynamics by Doppler ultrasound has been widely used. Absent end diastolic or reversed flow in the umbilical artery Doppler, brain sparing effect, altered aortic isthmus PI, and ductus venosus (DV) wave abnormalities are important signs for optimizing the delivery time.

In IUGR, changes in fetal hemodynamics occur in order to protect vital organs from hypoxia. The heart plays a central role in fetal adaptive mechanisms that underlie placental insufficiency, which includes a sequence of progressive changes in order to enable vascular and metabolic adaptation. Therefore, several Doppler echocardiographic parameters have been proposed to assess the central pathophysiological changes in early- (<32 weeks' gestation) and late-onset IUGR [5]. Increased values of myocardial performance index (MPI) can provide subclinical evidence of myocardial cell damage (fetal acidemia) and have been proposed to be predictors of adverse perinatal outcomes in early-onset IUGR, since they are useful tools to establish the difference between small-for-gestational age fetuses and late-onset IUGR [6, 7]. Subsequently, DV reversed A-wave and umbilical vein pulsations are considered strong predictors for fetal deterioration [8, 9]. Since the subclinical cardiac dysfunction is present from early stages of fetal deterioration, the assessment of fetal diastolic function is an important tool that might help to predict perinatal outcomes [10, 11].

In progressive placental insufficiency, the improvement of inferior vena cava with left ventricle (LV) preferential cardiac output contributes to a decreased LV compliance and causes an increase in left atrial (LA) pressure. As pulmonary vein Doppler reflects changes in LA pressure, the Pulmonary vein pulsatility index (PVPI) is a good parameter to assess atrial dynamics. Furthermore, despite the protective redistribution of oxygenated blood toward the heart, fetal hypoxia can result in cell damage and can be documented by reverse pulmonary vein A-wave, similar to the Doppler pattern flow of DV [12]. PVPI is an easily obtained Doppler parameter that can be useful for the evaluation of the left heart in IUGR. The aim of this study is to test the hypothesis that the PVPI is an early marker of cardiac dysfunction in IUGR fetuses with placental insufficiency.

Methods

This is a prospective, observational cross-sectional study that included 86 fetuses with gestational age ranging from 25 weeks to term. The participants with singleton pregnancies were recruited from 2 tertiary centers of Fetal Cardiology. The sample size was calculated based on a previous study on PVPI in IUGR in order to enable a difference between cases and controls with 20% power and 5% significance with 20 in each group. The sample was divided into 3 groups. The first group included 30 pregnant women whose fetuses were diagnosed with IUGR due to placental insufficiency. The second group included 28 fetuses with appropriate for gestational age (AGA) from hypertensive mothers (hypertensive disorders of pregnancy and chronic arterial hypertension). The third group included 28 fetuses with AGA from healthy mothers (controls). The inclusion criteria were as follows: normal fetal anatomy and known gestational age based on the date of the last menstrual period and confirmed by first trimester ultrasound. Fetuses with weights below 10th percentile according to according to WHO growth curves were considered as IUGR [13]. The criteria for placental dysfunction were Doppler signs of increased uteroplacental vascular impedance (increased umbilical artery systole/diastole ratio and either uterine or umbilical artery PI >2 SD above mean for gestational age). Chronic and gestational hypertensions were defined as blood pressure ≥140 mm Hg systolic or 90 mm Hg diastolic in pregnant women [14]. Cases of multiple fetuses, gestational age below 25 weeks, inadequate ultrasonic images, and with other structural or functional fetal abnormalities were excluded. At delivery, gestational age, birth weight, birth weight percentile, Apgar score, mode of delivery, and pregnancy complications were recorded. One newborn was excluded from IUGR group due to a structural abnormality and 2 others were excluded because their birth weights were higher than the 10th percentile for gestational age (discordance between fetal and birth weights). The Institutional Ethical Committee of both participating centers approved this study. Informed consent was obtained in all cases.

All women included in this study were examined only once using ultrasound and echocardiography equipment with 3.0–5.0 MHz convex transducers, presets for obstetrics and fetal cardiology, 2D/3D/4D images, M-mode, and Doppler modes (pulsed, continuous, power, and color mapping). Obstetric ultrasound was performed in all pregnant women to assess fetal morphology, amniotic fluid, and fetal biometry. Fetal weight estimation was performed according to the method of Hadlock et al. [15]. Diagnosis of IUGR was considered when the fetal weight was below the 10th percentile for gestational age, using fetal growth curves and classified as severe in those with body weight below the third percentile [13].

Color flow mapping was used to locate and enable the use of pulsed Doppler and the following parameters were evaluated: free loop umbilical artery of the umbilical cord, middle cerebral artery, and the uterine arteries [16]. Venous and arterial flows were studied and PI indexes of the arterial vessels (umbilical, middle cerebral, and uterine arteries) were obtained with an angle of insonation below 20°. The average of 3 Doppler measurements was considered with fetuses in apnea and no body movements.

Fetal echocardiographic examinations were performed at the same time as the obstetric Doppler in all pregnant women. To analyze the pulmonary venous flow, the Doppler sample volume was placed at the right superior pulmonary vein adjacent to the veno-

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atrial junction ("distal position") in a 4-chamber view, guided by color-flow mapping or power-angio Doppler [17] with an angle of insonation <30°. Scales of 0–20 cm/s and filters of 50–100 Hz were used and 3 measurements were obtained in apnea. In all fetuses, the PVPI (peak velocity [systolic or diastolic] minus pre-systolic velocity/mean averaged maximum velocity) was calculated after manual tracing of the pulmonary venous flow waveform. In groups 1 and 2, the DV flow was identified from a transverse section of the fetal abdomen at the level of the insertion of the umbilical cord. The sample volume was placed on the isthmus of the DV and DV pulsatility index (DVPI) was calculated in the same way as the pulmonary veins [18]. All records were stored in Digital Imaging and Communications in Medicine (DICOM) format and exported to CD and DVD for calculation of the intra- and inter-observer variability in 10 samples of each group [19].

Statistical Analysis

The data were transferred to Excel (Microsoft Excel 2010) and the statistical package SPSS version 18 was used for data analysis. Quantitative analysis were expressed as mean and SD. Analysis of variance and post-hoc Tukey test were used for the assessment of differences between the groups. Pearson's correlation was applied to examine the correlation between PVPI and DVPI and cerebroplacental ratio (CPR). Bland-Altman test was used to show the mean intra- and interobserver differences between the measurements (10 samples from each group). p values <0.05 were considered significant.

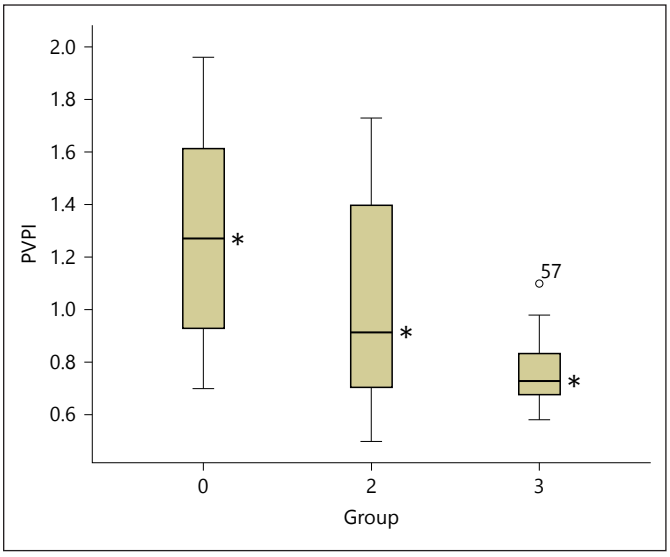

Fig. 1. Comparison of pulmonary vein pulsatility index (PVPI) between IUGR fetuses (group 1) with fetuses with normal growth (AGA) from hypertensive mothers (group 2) and from healthy mothers (group 3). Horizontal bars above and below median boxes represent maximal and minimal values of PVPI. * PVPI mean values.

Results

The study sample included 84 pregnant women, divided into 3 groups: group 1 included 27 fetuses with IUGR, group 2 included 28 fetuses with adequate weight for gestational age from pregnant women with hypertensive disorder, and group 3 included 28 fetuses with adequate weight for gestational age from healthy women (controls). Mean maternal age was 27 ± 6.5 years in group 1 (IUGR), 34 ± 6.7 years in group 2, and 32 ± 6.5 years in group 3, with mothers in IUGR group significantly younger as compared to other groups ($p < 0.01$). Mean gestational age was 31.4 ± 3 weeks in cases with IUGR, 30.0 ± 2 weeks in fetuses with AGA from hypertensive mothers, and 29.0 ± 2 weeks in controls ($p = 0.22$ in group 1 vs. control and $p = 0.2$ in group 2 vs. control group). The mean PVPI was significantly higher in group 1 (1.27 ± 0.39) than in group 2 (1.02 ± 0.37), $p = 0.01$, or group 3 (0.76 ± 0.12), $p < 0.001$ (Fig. 1). The pulmonary vein Doppler pattern is shown in Table 1a. The CPR was significantly lower (1.29 ± 0.68) in group 1 than in groups 2 (1.78 ± 0.41) and 3 (1.72 ± 0.29; $p = 0.001$). Uterine, umbilical, and middle cerebral arteries and pulmonary vein PI are shown in Table 1b. In the IUGR group, there was no significant correlation between PVPI and DVPI ($r = 0.05$; $p = 0.79$), or between PVPI and CPR (CPR = middle cerebral artery pulsatility index/umbilical artery pulsatility index; $r = 0.01$, $p = 0.97$; Fig. 2). However, in group 2, a moderate correlation between PVPI with DVPI was found, but not between PVPI and CPR (Fig. 2, 3). Intra-class and inter-class correlations, calculated from repeated measurements, were 0.91 and 0.88, respectively (Fig. 4, 5).

Discussion

Fetal cardiac function is routinely assessed in fetuses with congenital heart diseases. Recently, functional echocardiography has been employed in fetuses with extra cardiac conditions, such as IUGR, and can provide important information for clinical management decisions. Furthermore, considering that IUGR fetuses have adverse remodeled hearts (more globular) that lead to long-term adverse consequences in later life, the evaluation of cardiac function by fetal echocardiography enables cardiovascular prevention [20]. Measurements of ventricular contractility (shortening and ejection fraction), MPI, systemic venous, and umbilical venous (DV and umbilical venous) Doppler flow patterns are commonly used in the assessment of cardiac function by ultrasound. These parameters are considered to be strong predictors of perinatal mortality, but they are usually altered only in late stages of fetal

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Table 1.

a. Comparison of pulmonary vein pattern between IUGR fetuses (group 1) and AGA fetuses from hypertensive and healthy mothers (groups 2 and 3)

PV waves	Group 1 (IUGR)	Group 2	Group 3 (controls)	*p* values
PV S-wave	0.25±0.07[a]	0.29±0.07[b, c]	0.25±0.44[a, c]	0.033
PV D-wave	0.22±0.06	0.25±0.06	0.23±0.05	0.150
PV A-wave	0.11±0.03[a]	0.13±0.04[a, c]	0.14±0.02[b, c]	0.009

Values are mean ± SD.

S, systolic peak; D, diastolic peak; A, presystolic velocity. *p* values of pulmonary veins: [a, b, c] no significant differences = equal letters and significant differences = different letters.

AGA, appropriate growth for gestational age; PV, pulmonary vein.

b. PI values of pulmonary vein and uterine, umbilical, and medium cerebral arteries in groups 1, 2, and 3

PI	Group 1	Group 2	Group 3	*p* values
Uterine arteries	1.3±0.5	1.1±0.4	0.67±0.1	0.01
Umbilical artery	1.38±0.3	1.2±0.2	0.95±0.1	<0.001
MCA	1.7±0.4	1.9±0.3	1.8±0.2	0.007
PV	1.27±0.39[a]*	1.02±0.37[b]*	0.76±0.12	<0.001

PI values are mean ± SD. *p* values of pulmonary veins: [a]* group 1 versus and group 2 [b]* versus group 3: [a]* $p < 0.01$, e[b]* $p = 0.01$.

MCA, medium cerebral artery; PV, pulmonary vein.

deterioration. The assessment of pulmonary veins reflects LV compliance and LA pressure and may provide early information about myocardial dysfunction in IUGR, since LV dysfunction precedes right ventricle functional abnormalities. In this study, we observed that the Doppler pattern of the pulmonary vein flow in IUGR group was different than in the other groups with lower S- and A-wave velocities and an increased PVPI (Table 1a). The increase in LA pressure with consequent reduction of the A-wave velocity in the pulmonary vein could explain the elevation of PVPI. This phenomenon may be secondary to decreased LV compliance or to the abnormal LA dynamics in IUGR due to redistribution of flow.

Traditionally, the analysis of inflow pattern by conventional Doppler or tissue Doppler imaging (TDI) are sensitive tools for detecting cardiac diastolic dysfunction. In IUGR, inflow Doppler flow velocities are lower mitral E' velocities with higher E'/A ratios [10, 21]. Similarly, early-onset IUGR fetuses display an increased relaxation time in the early stages of deterioration, probably reflecting fetal adaptive mechanisms to chronic hypoxia in placental insufficiency. Thus, it has already been demonstrated that an increased MPI is associated with cell damage and that, in combination with retrograde shunting at

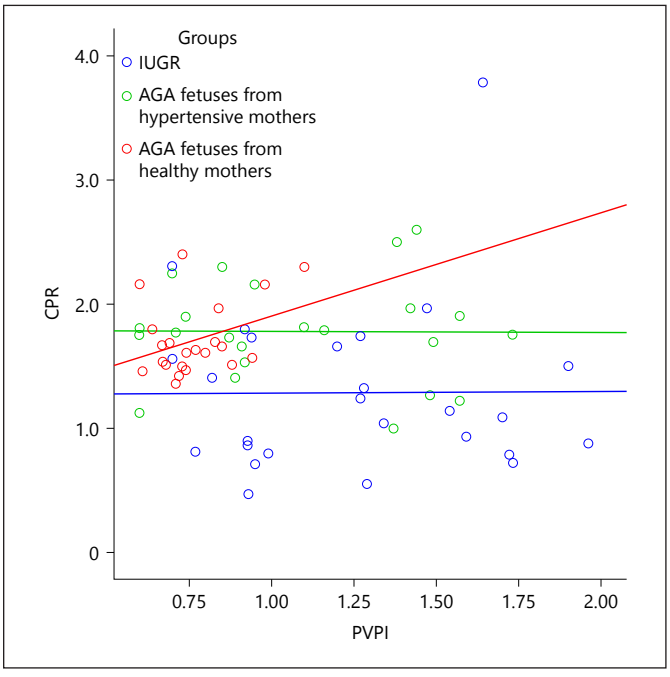

Fig. 2. Correlation between PVPI and CPR. $r = 0.01$, $p = 0.97$. PVPI, pulmonary vein pulsatility index; AGA, appropriate for gestational age; IUGR, intrauterine growth restriction; CPR, cerebroplacental ratio.

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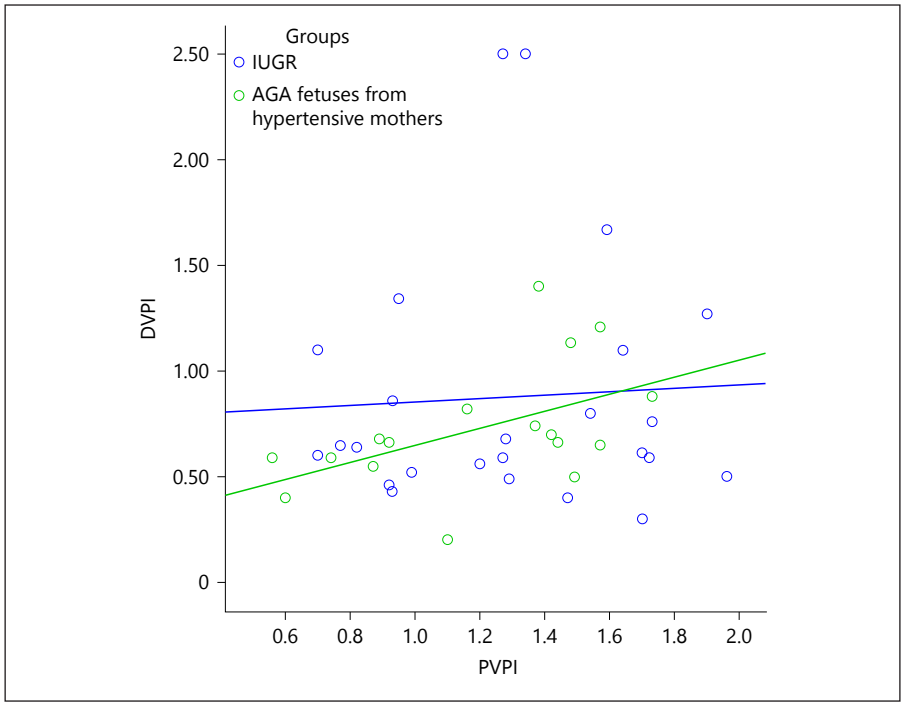

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Fig. 3. Correlation between PVPI and DVPI. $r = 0.05$, $p = 0.79$. PVPI, pulmonary vein pulsatility index; AGA, appropriate growth for gestational age; IUGR, intrauterine growth restriction; DVPI, ductus venosus pulsatility index.

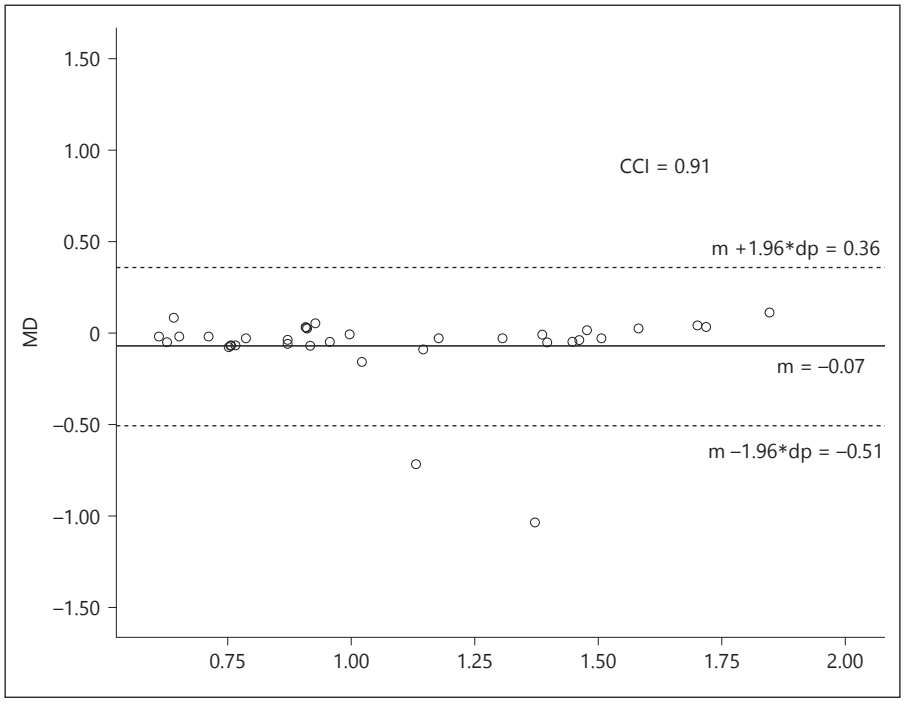

Fig. 4. Bland-Altman plots showing intraobserver variation in measurements of PIPV. PIPV, pulsatility index of pulmonary vein; m, mean; MD, mean difference between the measurements made by the same observer in; CCI, confidence interval; dp, standard deviation.

the aortic isthmus and DV, might be useful for predicting fetal deterioration, particularly in severe IUGR [22, 23]. Quantitative assessment of circulatory changes is done in the fetal aortic isthmus during progressive resistance to umbilical blood flow [23, 24].

The evaluation of the tricuspid and mitral annular displacement (TAPSE and MAPSE), by assessment of M-mode techniques, reflects global longitudinal function and has been shown to be altered in early stages of cardiac dysfunction, differently from the ejection fraction

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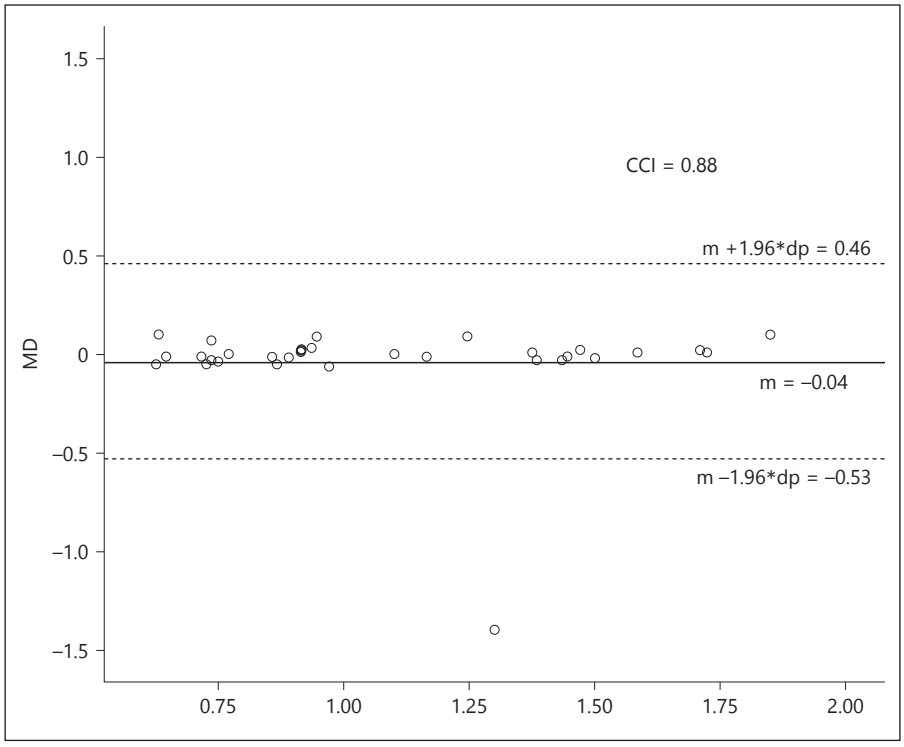

Fig. 5. Bland-Altman plots showing interobserver variation in measurements of PIPV. PIPV, pulsatility index of pulmonary vein; m, mean; MD, mean difference between the measurements made by 2 observers in; CCI, confidence interval; dp, standard deviation.

[25, 26]. Prospectively, systemic and umbilical venous Doppler flow abnormalities can predict adverse perinatal outcomes and are considered to be strong predictors of stillbirths in IUGR [27, 28]. Similarly to DV flow, the reversed pulmonary vein A-wave reflects fetal hypoxia, but the applicability of pulmonary vein Doppler patterns for predicting outcomes of IUGR remains unknown [29]. In this study, the IUGR fetuses had a higher PVPI with normal DV flow, probably because they were not in late stages of deterioration. Additionally, a recent study on fetal atrial function by speckle tracking technique has shown that the right atrial function is preserved in cases of moderate chronic hypoxia due to placental dysfunction [30, 31]. In that study, strain and velocity were greater at the right atrial walls, compared with the left, and the increased DVPI was not associated with right atrial dysfunction. Similar to our study, many of these fetuses were not centralized [32]. Indeed, we found a moderate correlation between DVPI and PVPI in AGA from hypertensive mothers. Possible reasons for this correlation are the highly specific IUGR population due to placental dysfunction and the lack of stratification based on placental insufficiency in group 2.

The use of pulmonary vein PI in fetuses has been proposed as a good echocardiographic Doppler parameter to assess fetal cardiac dynamics [12, 29] since it reflects LA pressure changes and is reproducible [17]. IUGR fetuses showed an increased PVPI, reflecting flow distribution in the left heart with changes in LA pressure, probably due to left ventricular dysfunction. In this study, we demonstrated that the PVPI is increased in fetuses with IUGR due to placental insufficiency.

The elevated impedances in uterine arteries in IUGR and AGA fetuses from hypertensive mothers, when compared to controls, were expected. We also found a reduced CPR in IUGR group, but not as a result of decreased MCA PI. Since many of these fetuses were not centralized, these results might suggest hemodynamic changes with preferential flow to the brain secondary to hypoxia. Therefore, we have not found any correlation between PVPI and CPR in IUGR.

In conclusion, this study demonstrated that fetuses with IUGR due to placental insufficiency show an increased PVPI when compared to AGA fetuses from hypertensive mothers and from healthy mothers, reflecting altered left heart dysfunction. This parameter could be used as an early predictor of cardiac dysfunction in IUGR, even before the expected late increase in DV impedance. Since other several diastolic cardiac function parameters involving atrial function have been proposed, they could also be useful as predictor of perinatal mortality [33].

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