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Transitional haemodynamic profiles of intrauterine growth-restricted preterm infants: correlation with antenatal Doppler characteristics

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BACKGROUND AND AIM: Intrauterine growth restriction (IUGR) with fetal Doppler abnormalities can lead to persistent haemodynamic adaptations. We aimed to investigate the association between antenatal Doppler characteristics and transitional haemodynamic profiles in IUGR preterm infants.
METHODS: Infants <1500 g were enrolled in this prospective cohort study. Over the first 72 h of life, stroke volume (SV), cardiac output (CO), cardiac contractility (ICON), heart rate, systemic vascular resistance (SVR), perfusion index (PI), peripheral oxygen saturation, cerebrovascular reactivity, cerebral oxygenation and oxygen extraction were monitored combining near-infrared spectroscopy, pulse-oximetry and electrical velocimetry. Using multivariate linear models, these parameters were compared between neonates with normal antenatal Doppler and abnormal umbilical Doppler without brain-sparing (UAbs-), with brain-sparing (UAbs+) or with abnormal ductus venosus flow (UA+DV).
RESULTS: Ninety-two neonates (9 UAbs-, 12 UAbs+ , 6 UA+DV, 65 controls) were included. Compared to controls, UAbs+ had higher CO ($p = 0.036$), ICON ($p < 0.001$) and SVR ($p = 0.012$), whereas UA+DV showed lower SV ($p = 0.038$), CO ($p = 0.018$), PI ($p = 0.006$) and the highest SVR increase ($p < 0.001$). Impaired cerebrovascular reactivity was observed in UAbs+ ($p < 0.001$) and UA+DV neonates ($p < 0.001$).
CONCLUSIONS: Antenatal Doppler abnormalities are associated with distinct transitional cardiovascular and cerebrovascular profiles in IUGR infants, with potential clinical implications.

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IMPACT:

- This study describes the association between specific antenatal Doppler abnormalities and distinct postnatal cardiovascular and cerebrovascular profiles in IUGR preterm infants.
- Knowledge of this association may aid to identify IUGR neonates at higher risk for complications and to develop individualised therapeutic approaches based on antenatal Doppler characteristics.
- Available literature investigating postnatal haemodynamics in IUGR infants is based on intrauterine growth or ponderal criteria that may underestimate the prevalence of fetal Doppler abnormalities and their hemodynamic consequences.
- This study provides a comprehensive haemodynamic overview across multiple districts, supporting the feasibility of non-invasive multimodal monitoring for neonatal hemodynamic assessment.

INTRODUCTION

Intrauterine growth restriction (IUGR) due to early-onset placental insufficiency is a common cause of iatrogenic premature delivery.[1] As suggested by the increased rates of mortality and morbidity reported in IUGR preterm infants,[2–6] this condition can further add to the harmful consequences of prematurity.

Doppler velocimetry of fetal arteries provides important information on fetoplacental haemodynamics and fetal well-being in the presence of placental insufficiency.[7] The sequence of Doppler abnormalities reflects worsening stages of fetoplacental disease. In particular, absent or reversed end-diastolic flow in the umbilical artery (UA) is an early marker of fetal hypoperfusion and

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hypoxia,[8,9] to which growth-restricted fetuses can adapt with a compensatory blood flow redistribution towards such vital organs as the heart and the brain. This cardiovascular remodeling, also defined as brain-sparing adaptation, is characterized by the evidence of reduced vascular resistances at Doppler assessment of the fetal middle cerebral artery (MCA).[10] If placental insufficiency further worsens, the brain-sparing adaptation may fail to support fetal circulation, leading to an impaired venous return and subsequent Doppler abnormalities in the ductus venosus (DV), which are a harbinger of impending fetal demise.[5]

According to the available literature on IUGR preterm neonates, cardiovascular adaptation to placental insufficiency may persist after birth,[11] with potential long-term implications.[12–15] The relationship between specific fetal Doppler characteristics and comprehensive postnatal haemodynamic features, however, has not been fully elucidated.

This study aimed to characterize cardiovascular and cerebrovascular profiles of IUGR preterm infants, assessed through multimodal haemodynamic monitoring during the transitional period, and to evaluate their association with antenatal Doppler abnormalities.

METHODS

Subjects

Preterm infants with a birthweight <1500 g or with a gestational age (GA) < 32 weeks admitted to the Neonatal Intensive Care Unit of IRCCS AOUBO, Bologna (Italy) between February 2018 and January 2024 were consecutively enrolled in this observational prospective study. Known genetic abnormalities or major congenital malformations, including congenital heart disease, were exclusion criteria. Due to the known influence of these conditions on the study parameters, infants with perinatal asphyxia, pulmonary hypertension requiring inhaled nitric oxide, severe anemia (defined as hematocrit <30%) and intraventricular hemorrhage (IVH) ≥ grade III were also ruled out. The study, approved by S. Orsola University Hospital Ethics Committee, Bologna, Italy (protocol no. 328/2017/O/Oss), was conducted in conformity with principles and regulations of the Helsinki Declaration. Written informed consent was obtained from the infants' parents/legal guardians.

Multimodal haemodynamic measurements

A continuous multiparametric monitoring platform was utilized during the first 72 h after birth as part of the local clinical practice using the following devices:

- Pulse oximetry (Radical 7; Masimo Corporation, Irvine, CA, sampling frequency 0.5 Hz) with neonatal sensors (RD SET™ NeoPt) placed on the right wrist to obtain peripheral arterial oxygen saturation (SpO_2, %), peripheral perfusion index (PI, %) and heart rate (HR, bpm).
- Electrical velocimetry (ICON®, Osypka Medical, Berlin, Germany, sampling frequency beat-to-beat) with neonatal sensors (iSense Electrical Cardiometry Skin Sensors, Osypka Medical, Berlin, Germany) applied as per manufacturer recommendations to obtain the following parameters: HR; weight-indexed cardiac output (CO, l/kg/min); weight-indexed stroke volume (SV, ml/kg); weight-indexed cardiac contractility index (ICON, a.u.); systemic vascular resistance, indexed for the infants' body surface area (SVR, dyn*s/cm^5/m^2).
- Near-infrared spectroscopy oximeter (INVOS 5100, Medtronic, Boulder, CO, sampling frequency 1 Hz), with disposable neonatal sensors placed on the infants' forehead, to obtain cerebral oxygenation ($CrSO_2$, %).

These devices were connected via a RS232 cable to a laptop running ICM + ® software (Cambridge Enterprise, UK) for real-time synchronized collection of multiparametric data. ICM+ was also used for the computation of cerebral fractional oxygen extraction (cFTOE = [SpO_2–$CrSO_2$]/SpO_2) and of the moving correlation coefficient between 10-s averaged $CrSO_2$ and HR (TOHRx) over 5-min time windows. TOHRx is a non-invasive marker for cerebrovascular reactivity (CR) validated in the preterm population, with positive values indicating impaired CR.[16,17]

After the recording, the signal traces were reviewed; time periods with signal noise or coinciding with invasive procedures (e.g., endotracheal intubation, line placement) were considered artefactual and, as such, excluded from the data analysis. Daily averages of each study parameter were then calculated and used for statistical analysis.

Clinical data collection

Antenatal scans were reviewed for Doppler velocimetry data. According to the local protocol and in line with international guidelines,[18] if IUGR without associated congenital anomalies was diagnosed, follow-up ultrasound scans were performed every 2 weeks; if fetoplacental Doppler abnormalities were detected, the scans were repeated weekly and cardiotocographic monitoring was also performed. Sonographic assessments were performed using Voluson scanner (GE Healthcare, Milwaukee, WI) with a 3.5–5 MHz convex probe. During each evaluation, amniotic fluid volume, fetal biometry and Doppler features of uteroplacental arteries, UA, MCA and DV were assessed.[19] Brain-sparing was defined by a pulsatility index <5th percentile for GA in the MCA. In the presence of Doppler abnormalities, indications for preterm delivery were customized for each pregnancy based on maternal status or in the presence of worsening fetal Doppler indexes or abnormal cardiotocographic monitoring. Based on their antenatal Doppler features, the enrolled infants were allocated to the following study groups: normal Doppler (controls); abnormal UA Doppler without brain-sparing (UAbs-); abnormal UA Doppler with brain-sparing (UAbs+); abnormal Doppler in the UA and in the DV (UA+DV).

Neonatal data included birthweight, GA, small-for-GA (SGA, defined by birthweight <10th percentile for GA), antenatal steroids administration (complete course vs. incomplete course or not given), Apgar score at 5 min, respiratory support (invasive vs. non-invasive ventilation or self-ventilating in air) and ongoing cardiovascular drugs on day 1, 2, and 3 of life. During the monitoring period, daily cranial and echocardiographic scans were performed using an ultrasound scanner CX50 (Philips Healthcare, Amsterdam, The Netherlands) with a convex 8–5 MHz probe and with a linear 12-MHz probe, respectively, to check for IVH development and to evaluate the ductal status. A haemodynamically significant patent ductus arteriosus (hsPDA) was defined by an internal ductal diameter ≥1.5 mm or a ductal diameter-to-left pulmonary artery ratio ≥0.5 and ≥1 among left atrium-to-aortic root ratio ≥1.5, ductus flow velocity ≤2.5 m/s, left pulmonary artery diastolic flow velocity >0.2 m/s or reversed diastolic flow in peripheral vessels (cerebral arteries and/or descending aorta).[20] The daily ductal status (hsPDA vs. restrictive or closed duct) was also recorded and used for statistical analysis.

Statistical analysis

The normal distribution of data was confirmed by the Kolmogorov-Smirnov test. Numerical variables were summarized as mean ± standard deviation or median (interquartile range) according to their distribution; categorical variables were summarized as frequencies and percentages. Kruskal–Wallis test and chi-squared test were used to compare clinical characteristics between the study groups.

The effect of different fetal Doppler features on each study parameter was evaluated building multivariable repeated-measures linear mixed-effects models (LMMs), which accounted for the repeated measures (day 1 = 0–24 h after birth; day 2 = 24–48 h after birth; day 3 = 48–72 h after birth) within each subject. Clinical factors that differed significantly between the study groups (i.e., GA, uteroplacental Doppler) or with a possible influence on the study parameters (i.e., hsPDA, cardiovascular drugs, hematocrit) were included as covariates. Since the ductal status and ongoing cardiovascular treatments changed over the study period, these variables were handled as time-dependent covariates, which means that their daily status was associated with the related daily-averaged values of each parameter.

The variance inflation factor (VIF) was used to assess multicollinearity between the model terms; the mean VIF of each LMM was <5 (CO:1.43; SV:1.43; ICON:1.43; SVR:1.44; HR:1.44; PI:1.44; SpO_2:1.54; TOHRx:1.54; $CrSO_2$:1.56; cFTOE:1.56), indicating low correlation between model predictors. Two sensitivity analyses, one excluding infants with IVH grade 1–2[21] and the second excluding SGA infants from the control group were also performed. Data were analyzed using IBM SPSS for Macintosh, version 28.0 (Armonk, NY:IBM Corp). Significance level was set at 0.05, and all tests were two-tailed.

RESULTS

Of 92 infants included (enrollment flow chart available as Supplementary Material), 65 (71%) had normal fetal Doppler, 9 (10%) had abnormal UA Doppler without brain-sparing, 12 (13%)

Table 1. Pre- and perinatal characteristics of the study population and results of between-group comparisons; significant pairwise comparisons at Bonferroni post-hoc test are highlighted as follows: *= p 0.038; ^= p 0.014.

	Normal Doppler ($n = 65$)	UAbs-($n = 9$)	UAbs+ ($n = 12$)	UA+DV ($n = 6$)	*P*-value
Gestational age (weeks), median (IQR)	29.8 (27.1–31.4)*	31.8 (30.8–32.4)*	31 (28.7–31.5)	30.5 (27.4–31.3)	**0.046**
Birth weight (g), median (IQR)	1284 (990–1492)^	1131 (1122–1147)	1048 (804–1283)	749 (727–877)^	**0.007**
Sex (males), *n* (%)	32 (49.2)	4 (44.4)	5 (41.7)	3 (50)	0.963
Twinhood, *n* (%)	13 (20)	4 (44.4)	4 (33.3)	2 (33.3)	0.341
Small for gestational age, *n* (%)	4 (6.2)	4 (44.4)	7 (58.3)	3 (50)	**<0.001**
Abnormal uteroplacental Doppler, *n* (%)	13 (20)	5 (55.6)	7 (58.3)	5 (83.3)	**<0.001**
Antenatal steroids (complete course), *n* (%)	44 (67.7)	7 (77.8)	11 (91.7)	5 (83.3)	0.325
Delivery mode (C-section), *n* (%)	55 (84.6)	9 (100)	12 (100)	6 (100)	0.198
Apgar score at 1′ median (IQR)	6 (5–8)	7 (6–9)	7 (5–8)	8 (7–8)	0.272
Apgar score at 5′, median (IQR)	9 (8–9)	9 (9–10)	9 (8–9)	9 (9–9)	0.081
Hematocrit at admission (%), median (IQR)	46.3 (42.4–49.7)	49.1 (48.4–50.5)	48.7 (46.5–50.6)	45.8 (45.5–56.7)	0.062

UAbs- abnormal umbilical artery Doppler without brain-sparing, *UAbs+* abnormal umbilical artery Doppler with brain-sparing, *UA+DV* abnormal umbilical artery and ductus venosus Doppler.
Significant comparisons are highlighted in bold.
*p= 0.043, post-hoc comparison.
^p= 0.017, post-hoc comparison.

Table 2. Clinical characteristics of the study population during the study period and results of between-group comparisons, performed using Chi-square tests for each day of life.

	Normal Doppler ($n = 65$)	UAbs-($n = 9$)	UAbs+ ($n = 12$)	UA + DV ($n = 6$)	*P*-value
Mechanical ventilation, *n* (%)					
Day 1	17 (26.2)	0 (0)	4 (33)	1 (16.7)	0.288
Day 2	18 (27.7)	0 (0)	2 (16.7)	1 (16.7)	0.270
Day 3	18 (27.7)	0 (0)	1 (9.1)	1 (16.7)	0.167
hsPDA, *n* (%)					
Day 1	33 (50.8)	3 (33.3)	8 (66.7)	3 (50)	0.511
Day 2	25 (38.5)	2 (22.2)	3 (25)	2 (33.3)	0.676
Day 3	10 (15.4)	2 (22.2)	1 (9.1)	1 (16.7)	0.882
Dopamine, *n* (%)					
Day 1	10 (15.4)	0 (0)	0 (0)	1 (16.7)	0.295
Day 2	10 (15.4)	1 (11.1)	1 (8.3)	1 (16.7)	0.915
Day 3	8 (12.3)	2 (22.2)	0 (0)	1 (16.7)	0.478
Dobutamine, *n* (%)					
Day 1	16 (24.6)	2 (22.2)	3 (25)	1 (16.7)	0.976
Day 2	16 (24.6)	2 (22.2)	3 (25)	1 (16.7)	0.976
Day 3	13 (20)	0 (0)	1 (8.3)	1 (16.7)	0.413

hsPDA hemodynamically significant patent ductus arteriosus, *UAbs-* abnormal umbilical artery Doppler without brain-sparing, *UAbs+* abnormal umbilical artery Doppler with brain-sparing, *UA+DV* abnormal umbilical artery and ductus venosus Doppler.

had abnormal UA Doppler with brain-sparing, and 6 (7%) abnormal UA+DV Doppler with brain-sparing. All the cases of fetal Doppler abnormalities were associated with early-onset IUGR.[22] Prenatal and perinatal characteristics of the study groups and between-group comparisons are provided in Table 1. Compared to controls, UAbs- infants had higher GAs ($p = 0.038$), whereas those with abnormal UA+DV Doppler had lower birthweight ($p = 0.014$). The proportion of SGA infants also varied significantly ($p < 0.001$), with the highest prevalence in the UAbs+ group (58.3%). Clinical and haemodynamic features during the study period are detailed in Table 2; the daily prevalence of hsPDA, need for invasive ventilation and treatment with cardiovascular drugs (i.e., dopamine and dobutamine) did not differ significantly among the study groups.

A total of 275 24-h epochs were analyzed for the study purposes; one infant interrupted the haemodynamic monitoring at 52 h of life due to his transfer in another ward.

LMMs results (available as Supplementary Material) showed no significant between-group difference in HR, SpO_2, $CrSO_2$ and cFTOE, while CO, SV, ICON, SVR, PI and TOHRx differed significantly. Compared to controls, UAbs+ neonates had significantly higher CO ($b = 0.049$, 95%CI:0.003–0.095, $p = 0.036$) and ICON ($b = 40.841$, 95%CI:17.832–63.850, $p < 0.001$), whereas those with UA+DV Doppler abnormalities showed significantly reduced

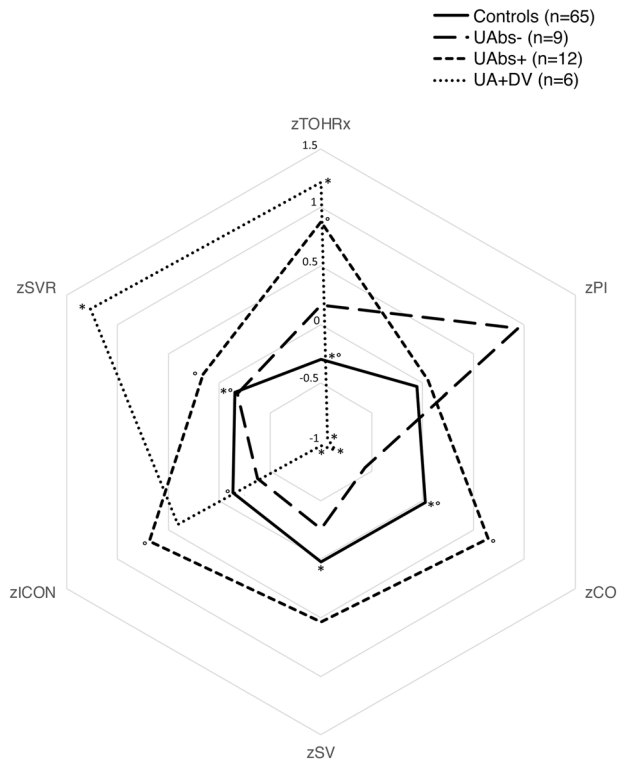

Fig. 1 Radar charts of cardiovascular and cerebrovascular hemodynamic profiles according to the antenatal status of fetal Doppler. The radial axis values indicate the estimated z-score means of the parameters included in the chart. Significant differences between UAbs+ and UA+DV vs. controls are highlighted with ° and *, respectively. zCO z-score of estimated cardiac output means, zPI z-score of estimated means of the perfusion index, zSV z-score of estimated stroke volume means, zICON z-score of estimated means of the contractility index, zSVR z-score of estimated means of systemic vascular resistance, zTOHRx z-score of estimated means of the correlation coefficient between cerebral oxygenation and heart rate.

SV ($b = -0.390$, 95%CI:−0.759;−0.021, p = 0.038), CO ($b = -0.049$, 95%CI:−0.090;−0.009, $p = 0.018$) and PI ($b = -0.120$, 95% CI:−0.207;−0.034, $p = 0.006$). SVR were significantly increased in UAbs+ ($b = 3.881$, 95%CI:0.876–6.885, $p = 0.012$) and, even more, in UA+DV infants ($b = 8.287$, 95% CI:4.170–12.404, $p < 0.001$) compared to controls. Similarly, more positive TOHRx values were observed in both UAbs+ ($b = 0.093$, 95%CI:0.045–0.140, $p < 0.001$) and UA+DV groups ($b = 0.103$, 95%CI:0.053–0.153, $p < 0.001$). No significant difference was observed between UAbs- and control infants. Two sensitivity analyses were performed, excluding seven infants with IVH grade 1–2 (of which five controls and two UAbs+) and four SGA infants from the control group; both analyses yielded unchanged LMMs results.

Figure 1 provides a graphical representation of postnatal haemodynamic profiles in relation to antenatal Doppler characteristics; z-scores of the estimated means obtained from each LMM were used for chart building.

DISCUSSION

According to the present results, progressive stages of fetoplacental vascular impairment are associated with distinctive cardiovascular and cerebrovascular profiles in IUGR preterm infants during postnatal transition.

The aberrant placentation underlying placental insufficiency leads to an inadequate vascular adaptation at the placental interface, with a progressive rise in vascular resistances. This, in turn, determines a chronic fetal hypoperfusion that manifests itself with IUGR and such compensatory haemodynamic changes as the brain-sparing vascular remodeling, characterized by a blood flow redistribution towards vital organs.

In line with available evidence of increased peripheral resistance and higher blood pressure in IUGR preterm infants,[23] we observed a significant increase in SVR in UAbs+ and UA+DV infants compared to control peers. Of note, an inverse correlation between birthweight and blood pressure, which depends on SVR, had been previously reported;[24] likewise, the greatest SVR increase occurred in UA+DV infants, who also had lowest birthweights. The chronic hypoxia to which IUGR fetuses are exposed elicits oxidative stress and chronic inflammation, with subsequent inhibition of vasodilatory pathways[25] and release of pro-inflammatory mediators potentially responsible for elastin depletion and increased vascular stiffness.[23] Moreover, the brain-sparing adaptation has been associated with an increased abundance of sympathetic nerve terminals on peripheral fetal vessels.[26] These structural changes likely contribute to the postnatal persistence of raised SVR in IUGR neonates with brain-sparing, and are proposed to underlie the long-known association between IUGR and arterial hypertension.[27] Whether postnatal SVR may correlate with blood pressure during childhood or adulthood, potentially predicting later cardiovascular risk, warrants prospective investigation.

The abovementioned increase in placental vascular resistance and fetal SVR progressively raises right ventricular afterload. On the other hand, the brain-sparing-related vasodilation of cerebral arteries decreases left ventricular afterload, shifting fetal CO in favor of the left ventricle to enhance vital organ perfusion.[28] In the present study, UAbs+ infants showed a significantly increased cardiac contractility and higher CO levels compared to controls, indicating a sustained enhancement of left ventricular output. These findings possibly result from the redistribution of fetal CO towards the left heart and are in line with echocardiographic evidence of hypertrophied hearts[29,30] and higher left ventricular output over the first postnatal days described in SGA neonates.[30–33] Of note, a programmed increase in IGF-2 expression in the myocardiocites of growth-restricted lambs, ensuing in left ventricular hypertrophy, has been reported as a potential adaptation to chronic hypoxia.[34]

If placental insufficiency further worsens, these adaptive cardiac changes ultimately fail to support fetal circulation, leading to a progressive heart failure with impairment of venous return that can be detected by DV velocimetry. The significant SV and CO decrease associated with the highest SVR values observed in UA+DV infants likely reflect the inability of the fetal heart to cope with sustained afterload increases, resulting in a marked myocardial dysfunction that persists beyond birth.[11,27,35–39] In turn, both reduced CO and increased SVR may contribute to the significant PI decrease observed in the UA+DV group. In preterm neonates, low PI values on the first day of life have been associated with low-flow status and with an increased risk of adverse neurological outcome.[40] Although further evidence is required to confirm this preliminary finding, we postulate that the combination of reduced left ventricular output, decreased peripheral perfusion and significantly raised SVR in UA+DV neonates may contribute to the development of ischemic complications frequently reported in this population (e.g., periventricular leukomalacia, necrotizing enterocolitis, intestinal perforation etc.).[3,5,14]

We found significantly more positive TOHRx values in UAbs+ and UA+DV infants independently from postnatal age, indicating a greater CR impairment if antenatal brain-sparing was present. This finding is consistent with limited available evidence of impaired cerebral autoregulation in SGA preterm infants.[41–43] The structural remodeling of cerebral vasculature described in animal models of chronic fetal hypoxia and characterized by increased wall thickness, decreased vascular contractility and reduced nitric oxide-mediated vasodilation[44] are likely responsible for CR

impairment in IUGR infants with brain-sparing. In turn, impaired CR may contribute to the increased rates of IVH, white matter injury and adverse neurodevelopment reported in infants with antenatal Doppler abnormalities.[4,6,14,45]

No significant $CrSO_2$ and cFTOE changes were observed in relation to different fetal Doppler features. To date, the assessment of these parameters in IUGR/SGA infants during postnatal transition has brought variable results: while several studies described increased $CrSO_2$ and lower cFTOE compared to controls,[46–48] others reported no difference[49] or even a possible sex-dependent effect with greater $CrSO_2$ in SGA males.[46,49] Methodological differences, such as the use of growth or ponderal criteria for IUGR/SGA classification, along with other influencing factors (e.g., varying hematocrit levels, which can affect oxygen carrying capacity and were therefore included in the LMM covariates for $CrSO_2$ and cFTOE), may have contributed to these varying findings.

The local Obstetric Unit is a referral center for placental-related pregnancy complications; this explains the relatively large prevalence of vascular IUGR in our cohort and represents a point of strength of the present study, as it allowed to obtain good-quality data on fetal Doppler and to examine the precise association between antenatal Doppler features and postnatal haemodynamic profiles, which not been previously investigated. Most of the available literature is in fact based on intrauterine growth or on ponderal criteria which, as the present data also suggest, may significantly underestimate the prevalence of Doppler abnormalities. Moreover, merging infants with different Doppler characteristics into a single IUGR group would have hindered the detection of the haemodynamic changes specifically associated with different stages of fetal Doppler impairment, such as the marked reduction of SV, CO, PI and the greatest SVR increase observed in UA+DV infants. Of note, the present data also suggest that antenatal brain sparing represents a hallmark for the development of meaningful postnatal haemodynamic changes, whereas if this adaptation was not evident, no significant differences were noted in both cardiovascular and cerebrovascular parameters compared to control infants.

Another unique strength of this study is the use of non-invasive comprehensive multimodal monitoring to assess multiple cardiovascular and cerebrovascular parameters continuously and simultaneously. The cardiovascular changes detected by electrical velocimetry are consistent with available echocardiographic evidence on IUGR/SGA neonates,[29–33] highlighting the potential role of this technique for neonatal haemodynamic monitoring. Furthermore, our finding of altered CR obtained with TOHRx is in line with previous data based on invasive CR indexes,[41–43] supporting the use of this completely non-invasive marker for CR assessment in the preterm population if arterial blood pressure monitoring is unavailable.

The selection of multiple hemodynamic parameters from different districts is in line with previous evidence supporting the role of a multimodal comprehensive monitoring for an individualized hemodynamic assessment in preterm infants,[50–52] and allowed us to shed light not only on the pathophysiological mechanisms underlying the observed findings (e.g., increased CO and SV secondary to enhanced heart contractility in UAbs-; maximal afterload increase with significant CO reduction and peripheral hypoperfusion in the UA+DV group), but also on their potential clinical implications (e.g., potentially increased risk of low flow complications in the presence of a combined reduction of CO and PI).

The relatively small number of all the subgroups with impaired antenatal Doppler and especially of UA+DV infants needs to be acknowledged as a study limitation which could potentially limit the generalizability of subgroup-specific findings. Nevertheless, the use of repeated-measures LMMs enabled adequate power analysis despite the relatively small number of cases, although further validation on larger prospective cohorts is needed to confirm these preliminary results.

This study describes the association between different stages of antenatal Doppler impairment and specific haemodynamic profiles in preterm infants during the transitional period. Knowledge of these profiles may bring useful information to stratify the cardiovascular and neurological risk of this frail population and to develop individualized haemodynamic approaches based on the underlying pathophysiology, with the ultimate goal of improving neonatal outcomes. Prospective follow-up evaluations are required to assess potential long-term ramifications of the present findings.

DATA AVAILABILITY

The study dataset and the statistical output of the study analyses are available upon reasonable request from the corresponding author (S.M.).

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AUTHOR CONTRIBUTIONS

S.M., A.N.D.G., and L.C. conceived the study. S.M., R.P., and M.A. enrolled the patients. S.M., A.N.D.G., M.A., and R.P. acquired the data. J.L. and S.M. performed the data analysis. M.C. and P.S. contributed to methodology and data acquisition. T.A., G.P., and L.C. contributed to data interpretation. S.M. and A.N.D.G. wrote the first draft of the manuscript. T.A., J.L., R.P., M.A., P.S., M.C., G.P., and L.C. critically revised the manuscript for important intellectual content. All the authors have approved the approved the final version of the manuscript submitted for publication and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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PATIENTS' CONSENT STATEMENT

The study protocol was approved by S. Orsola University Hospital Ethics Committee, Bologna, Italy (protocol no. 328/2017/O/Oss). Written informed consent for study participation was obtained from the parents/legal guardians of each patient.

COMPETING INTERESTS

P.S. and M.C. have a financial interest in a fraction of the licensing fees for the software ICM+ (through Cambridge Enterprise Ltd, Cambridge, UK), used in this research project. The other authors have no conflict of interest to disclose.

ADDITIONAL INFORMATION

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