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ORIGINAL RESEARCH ARTICLE

Comparison of ductus venosus Doppler and cerebroplacental ratio for the prediction of adverse perinatal outcome in high-risk pregnancies before and after 34 weeks

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Abstract

Introduction: The objective of the study was to compare the accuracy of the ductus venosus pulsatility index (DV PI) with that of the cerebroplacental ratio (CPR) for the prediction of adverse perinatal outcome at two gestational ages: <34 and ≥34 weeks' gestation.

Material and methods: This was a retrospective study of 169 high-risk pregnancies (72 < 34 and 97 ≥ 34 weeks) that underwent an ultrasound examination of CPR, DV Doppler and estimated fetal weight at 22–40 weeks. The CPR and DV PI were converted into multiples of the median, and the estimated fetal weight into centiles according to local references. Adverse perinatal outcome was defined as a composite of abnormal cardiotocogram, intrapartum pH requiring cesarean delivery, 5′ Apgar score <7, neonatal pH <7.10 and admission to neonatal intensive care unit. Values were plotted according to the interval to labor to evaluate progression of abnormal Doppler values, and their accuracy was evaluated at both gestational periods, alone and combined with clinical data, by means of univariable and multivariable models, using the Akaike information criteria (AIC) and the area under the curve (AUC).

Results: Prior to 34 weeks' gestation, DV PI was the latest parameter to become abnormal. However, it was a poor predictor of adverse perinatal outcome (AUC 0.56, 95% CI: 0.40–0.71, AIC 76.2, $p > 0.05$), and did not improve the predictive accuracy of CPR for adverse perinatal outcome (AUC 0.88, 95% CI: 0.79–0.97, AIC 52.9, $p < 0.0001$). After 34 weeks' gestation, the chronology of the DV PI and CPR anomalies overlapped, but again DV PI was a poor predictor for adverse perinatal outcome (AUC 0.62, 95% CI: 0.49–0.74, AIC 120.6, $p > 0.05$), that did not improve the CPR ability to predict adverse perinatal outcome (AUC 0.80, 95% CI: 0.67–0.92, AIC 106.8, $p < 0.0001$). The predictive accuracy of CPR prior to 34 weeks persisted when the gestational age at delivery was included in the model (AUC 0.91, 95% CI: 0.81–1.00, AIC

Abbreviations: AIC, Akaike information criteria; APO, adverse perinatal outcome; AUC, area under the curve; CPR, cerebroplacental ratio; CS-IFC, cesarean section for intrapartum fetal compromise; DV PI, ductus venosus pulsatility index; EFW, estimated fetal weight; EO-FGR, early-onset fetal growth restriction; GA, gestational age; LO-FGR, late-onset fetal growth restriction; MCA, middle cerebral artery; MoM, multiples of the median; NICU, Neonatal Intensive Care Unit; SGA, small for gestational age.

46.3, $p < 0.0001$, vs AUC 0.86, 95% CI: 0.72–1, AIC 56.1, $p < 0.0001$), and therefore was not determined by prematurity.

Conclusions: CPR predicts adverse perinatal outcome better than DV PI, regardless of gestational age. Larger prospective studies are needed to delineate the role of ultrasound tools of fetal wellbeing assessment in predicting and preventing adverse perinatal outcome.

KEYWORDS
adverse perinatal outcome, cerebroplacental ratio, ductus venosus Doppler, fetal Doppler

1 | INTRODUCTION

Current consensus indicates that late-onset fetal growth restriction (LO-FGR) is caused by an imbalance between fetal demands and placental supply,[1–3] in which hemodynamic anomalies occur regardless of fetal weight.[4–11] In pregnancies complicated by LO-FGR, adverse perinatal outcome (APO) is optimally predicted with the cerebroplacental ratio (CPR), that reflects the degree of cerebral vasodilation in response to placental relative insufficiency. Conversely, early-onset fetal growth restriction (EO-FGR) is caused by a progressive placental failure where prediction of APO is achieved using the estimated fetal weight (EFW)[12] and umbilical artery (UA) Doppler,[13,14] although with progressive hemodynamic deterioration, cerebral vasodilation also occurs, making CPR a potentially useful tool for the prediction of APO, along with EFW.[1]

In pregnancies complicated by EO-FGR, the ductus venosus (DV) Doppler has been considered as a marker of progression, but not in fetuses with LO-FGR, in which hemodynamic progression does not reach such degrees of severity. A drawback of this approach has been the paucity of information concerning the role of the DV Doppler at the end of pregnancy. Moreover, no study has clearly evaluated and compared the ability of the DV Doppler along with CPR in the prediction of APO prior to and beyond 34 weeks' gestation. Finally, even though the DV Doppler might be the last hemodynamic parameter to be altered, this does not necessarily make it the most accurate parameter for the prediction of APO, such that the veracity of such assertion remains to be proved.

The aim of this study was to compare the predictive accuracy of ductus venosus pulsatility index (DV PI) and CPR in the prediction of APO alone and combined with other sonographic or clinical parameters.

> **Key message**
>
> The best prediction of adverse perinatal outcome both prior to and beyond 34 weeks' gestation was achieved by means of cerebroplacental ratio multiples of the median evaluation. Addition of ductus venosus Doppler did not improve the predictive accuracy. However, prior to 34 weeks, it might provide useful information about fetal hemodynamic progression.

2 | MATERIAL AND METHODS

This was a retrospective study of 169 high risk pregnancies who attended La Fe public tertiary maternity hospital, between 2012 and 2022. These included cases with chronic hypertension, pre-eclampsia, previous stillbirth and reduced fetal growth. Other pregnancies were considered at risk for different reasons, such as reduced amniotic fluid, advanced maternal age, assisted reproduction, and reduced fetal movements.

The ultrasound examinations were performed between 22 and 41 weeks' gestation (72 prior to 34 and 97 at or beyond 34 weeks) and included an EFW, a Doppler evaluation of the UA and middle cerebral artery (MCA) pulsatility indices (PI), and an evaluation of the DV PI. The UA, MCA and DV were recorded for fetal surveillance using color and pulse Doppler according to earlier descriptions[15–17] and the cerebroplacental ratio (CPR) was calculated as the ratio between the MCA PI and the UA PI.[18] Only one (the last) examination per fetus was included. Pregnancies were followed until the onset of spontaneous labor, induction of labor or elective cesarean section for obstetric indications. Management of fetuses, hospital protocols, and rate of inductions and cesarean sections did not change during the study period.

EFW and birthweight values were converted into centiles,[19] while CPR and DV PI values were converted into multiples of median (MoM) dividing each value by the 50th centile at each gestational age as earlier described.[15,16] CPR and DV PI medians (50th centile) were calculated using these equations adjusting for GA (GA):

$$\text{CPR 50th centile} = -3.814786276 + 0.36363249 \times \text{GA} - 0.005646672 \times \text{GA}^2$$

$$\text{DV 50th centile} = 0.3718 + 0.01826 \times \text{GA} - 0.0004172 \times \text{GA}^2$$

Doppler assessment was performed by the first author, a certified expert in obstetric ultrasound by the Spanish Society of Obstetrics and Gynecology, using General Electric Voluson (E8/E6/730) ultrasound machines with 2–8 MHz convex probes, during

TABLE 1 Descriptive statistics of the two groups of fetuses: Left: Examined prior to 34 weeks, and right: Examined at or beyond 34 weeks' gestation.

	Prior to 34 weeks (*n* = 72)		At or beyond 34 weeks (*n* = 97)		
	Mean (SD)	Median (1st, 3rd Quartile)	Mean (SD)	Median (1st, 3rd Quartile)	*p*-value
Maternal age (years)	33.6 (5.6)	33.5 (30, 37.7)	33.15 (5.6)	34.0 (30, 37)	NS
Maternal pre-pregnancy weight (kg)	60.1 (13.9)	58 (51.7, 64.2)	60.3 (9.4)	58 (53, 67)	NS
Maternal height (cm)	162 (6.1)	161 (157, 167)	161 (6.4)	160 (157, 165)	NS
Maternal body mass index	23.3 (4.9)	21.5 (20.4, 24.5)	22.8 (3.5)	22.1 (20.3, 24.8)	NS
GA at examination (weeks)	30.2 (2.8)	31 (28.5, 32.3)	37.21 (1.6)	37.14 (36.2, 38.5)	<0.0001
EFW (hadlock-4) (g)	1125 (367.9)	1106 (814, 1405)	2319 (475)	2250 (1967, 2682)	<0.0001
EFW centile[a]	9.35 (23.9)	0 (0, 4)	10.8 (18.7)	3 (1, 11)	<0.001
CPR MoM	0.57 (0.33)	0.53 (0.31, 0.76)	0.84 (0.35)	0.84 (0.60, 1)	<0.0001
DV PIV MoM	1.37 (0.88)	1.2 (0.91, 1.52)	1.29 (0.57)	1.24 (0.96, 1.55)	<0.0001
GA at labor (weeks)	33.1 (4.05)	33.4 (30.0, 36.9)	38.6 (1.61)	38.86 (37.5, 39.79)	<0.0001
Interval exam-labor (days)	20.5 (24.7)	7 (2, 36.5)	9.7 (8.9)	8 (3, 14)	<0.0001
Birthweight (g)	1559 (767.7)	1348 (900, 1991)	2491 (507)	2500 (2100, 2775)	<0.0001
BW centile[a]	9 (22.2)	0 (0, 4.2)	10.7 (19.5)	2 (0, 12)	<0.001
Apgar at 5 min	9.2 (2)	10 (9, 10)	9.81 (0.46)	10 (10, 10)	<0.05
Arterial cord pH	7.04 (1.27)	7.27 (7.23, 7.30)	7.19 (0.76)	7.27 (7.22, 7.32)	NS
	N (%) 72		N (%) 97		
Adverse perinatal outcome	57 (79.2)		29 (29.9)		<0.0001
Nulliparous	45 (62.5)		55 (56.7)		NS
Gender male	41 (57)		51 (52.6)		NS
Apgar 5 min <7	0 (0)		0 (0)		NS
Arterial cord pH <7.10	3 (4.2)		4 (4.12)		NS
Onset of labor					
Spontaneous onset of labor	9 (12.5)		24 (24.7)		NS
Induction of labor	15 (20.8)		56 (57.7)		<0.0001
Fetal demise (>22 weeks)[b]	1 (1.4)		0 (0)		NS
TOP (≤22 weeks)[b]	1 (1.4)		0 (0)		NS
Elective cesarean section	47 (65.3)		17 (17.5)		<0.0001
Via of labor					
Spontaneous vaginal delivery	15 (20.8)		46 (47.4)		<0.001
Assisted vaginal delivery	2 (2.8)		15 (15.4)		<0.01
Cesarean section abnormal CTG	3 (4.2)		6 (6.2)		NS
Cesarean section dystocia	5 (6.9)		13 (13.4)		NS
Elective cesarean section	47 (65.3)		17 (17.5)		<0.0001
Neonate destiny					
Maternal ward	15 (20.8)		71 (73.2)		<0.0001
Neonates ward	48 (66.6)		26 (26.8)		<0.0001
NICU	7 (9.7)		0 (0)		<0.01
Postmortem study	2 (2.8)		0 (0)		NS

Abbreviations: BW, birthweight; CPR, cerebroplacental ratio; EFW, estimated fetal weight; FGR, fetal growth restriction; GA, gestational age; MoM, multiples of the median; SD, standard deviation; TOP, voluntary termination of pregnancy according to Spanish law.

[a]Centiles according to local population references (Hospital Clinic de Barcelona, Spain population references); CTG, cardiotocography, NICU, Neonatal Intensive Care Unit,

[b]These fetuses died prior to labor and went sent to postmortem study. One was a 26 weeks stillbirth, and the other a voluntary TOP at 22 weeks.

fetal quiescence (behabioural states 1F and 2F), in the absence of fetal tachycardia, and keeping the insonation angle with the examined vessels as small as possible.

GA was determined according to the crown-rump length in the first trimester. Multiple pregnancies and those complicated by fetal abnormalities or aneuploidy were excluded from the study. Demographic and pregnancy characteristics including, maternal age, parity, pre-pregnancy weight and height, were collected at the time of ultrasound assessment. Pregnancy outcomes including birthweight, mode of delivery, Apgar scores, cord arterial pH and admission to the neonatal ward or neonatal intensive care unit, were collected after birth to evaluate APO. This was considered when the outcome was adverse for any of these four components: (1) Cesarean section for abnormal intrapartum fetal heart rate (also called cesarean section for

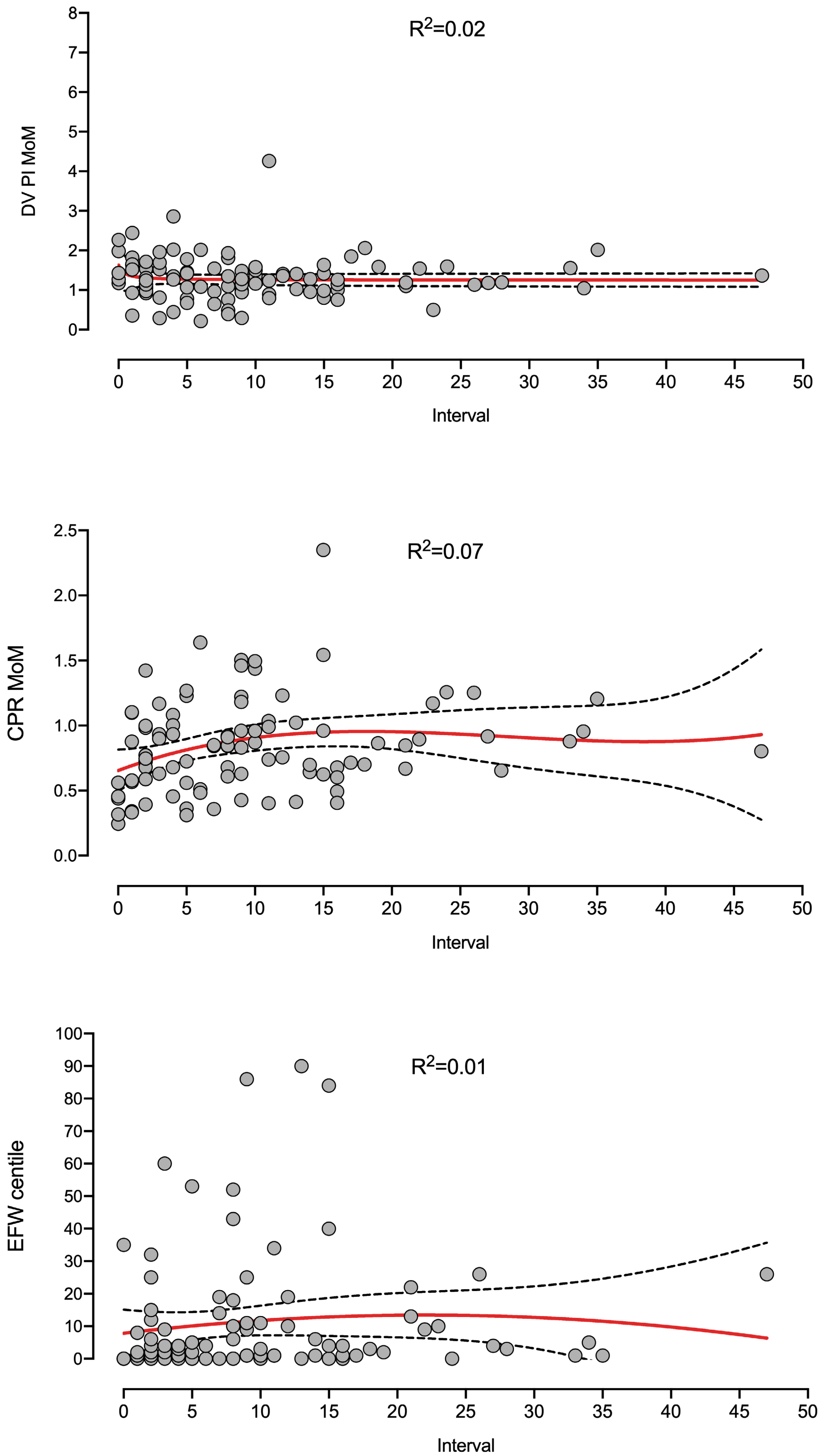

FIGURE 1 Ductus venosus (DV) pulsatility index (PI) multiples of median (MoM), cerebroplacental ratio (CPR) MoM and estimated fetal weight (EFW) centile values examined at, or beyond, 34 weeks' gestation, plotted against the interval to delivery. Interpolation curves and 95% confidence intervals (CI) showed a poor R^2 and did not suggest a clear chronology of progression to abnormality.

TABLE 2 Logistic regression models for the prediction of adverse perinatal outcome at or beyond 34 weeks, $N = 97$.

Model 1								
CPR MoM + DV PI MoM + EFW centile + maternal age + parity								
AUC (95% CI) 0.81 (0.71–0.92)								
AIC	104.7		Intercept	CPR MoM	DV PI MoM	EFW centile	Maternal age	Parity
p-value	<0.0001	*p*-value		<0.01	NS	<0.05	NS	NS
NPP (%)	84	Estimate	−0,05404	−311 271	0,53 171	−0,06484	0,02993	0,51 439
PPP (%)	77.3	OR		0.04	1.70	0.94	1.03	1.67
Model 2								
CPR MoM + DV PI MoM + EFW centile + maternal age								
AUC (95% CI) 0.81 (0.70–0.92)								
AIC	105.4		Intercept	CPR MoM	DV PI MoM	EFW centile	Maternal age	
p-value	<0.0001	*p*-value	NS	<0.01	NS	NS	NS	
NPP (%)	83.5	Estimate	−0,58 288	−285 467	0,40 924	−0,05411	0,05309	
PPP (%)	88.9	OR		0.05	1.50	0.95	1.05	
Model 3								
CPR MoM + DV PI MoM + EFW centile + parity								
AUC (95% CI) 0.82 (0.71–0.92)								
AIC	102.8		Intercept	CPR MoM	DV PI MoM	EFW centile	Parity	
p-value	<0.0001	*p*-value		<0.01	NS	<0.05	NS	
NPP (%)	84	Estimate	0,86 065	−314 105	0,58 634	−0,06576	0,56 529	
PPP (%)	77.3	OR		0.04	1.80	0.94	1.76	
Model 4								
CPR MoM + DV PI MoM + EFW centile								
AUC (95% CI) 0.82 (0.71–0.93)								
AIC	104.5		Intercept	CPR MoM	DV PI MoM	EFW centile		
p-value	<0.0001	*p*-value		<0.01	NS	NS		
NPP (%)	84.8	Estimate	105 050	−283 510	0,49 229	−0,05299		
PPP (%)	94.4	OR		0.059	1.63	0.95		
Model 5								
CPR MoM + DV PI MoM								
AUC (95% CI) 0.80 (0.68–0.93)								
AIC	107.1		Intercept	CPR MoM	DV PI MoM			
p-value	<0.0001	*p*-value		<0.001	NS			
NPP (%)	85	Estimate	0,93 528	−326 355	0,54 752			
PPP (%)	100	OR		0.038	1.73			
Model 6								
CPR MoM + EFW centile								
AUC (95% CI) 0.80 (0.69–0.92)								
AIC	103.7		Intercept	CPR MoM	EFW centile			
p-value	<0.0001	*p*-value		<0.01	NS			
NPP (%)	84.1	Estimate	165 302	−274 606	−0,05559			
PPP (%)	94.4	OR		0.064	0.94			
Model 7								
DV PI MoM + EFW centile								
AUC (95% CI) 0.76 (0.66–0.87)								
AIC	113.7		Intercept	DV PI MoM	EFW centile			
p-value	<0.0001	*p*-value		NS	<0.05			
NPP (%)	70.2	Estimate	−0,95 396	0,42 648	−0,06849			
PPP (%)	33.3	OR		1.53	0.93			

(Continues)

TABLE 2 (Continued)

Model 8						
DV PI MoM						
AUC (95% CI) 0.62 (0.49–0.74)						
AIC	120.6		Intercept	DV PI MoM		
p-value	NS	*p*-value		NS		
NPP (%)	69.8	Estimate	−154 861	0,52 628		
PPP (%)	0	OR		1.69		
Model 9						
EFW centile						
AUC (95% CI) 0.79 (0.68–0.90)						
AIC	112.6		Intercept	EFW centile		
p-value	<0.0001	*p*-value		<0.05		
NPP (%)	70.1	Estimate	−0,37 012	−0,07225		
PPP (%)	—	OR		0.93		
Model 10						
CPR MoM						
AUC (95% CI) 0.80 (0.67–0.92)						
AIC	106.8		Intercept	CPR MoM		
p-value	<0.0001	*p*-value		<0.001		
NPP (%)	85	Estimate	163 424	−323 053		
PPP (%)	100	OR		0.039		
Model 11						
CPR MoM + EFW centile + parity						
AUC (95% CI) 0.81 (0.70–0.91)						
AIC	102.4		Intercept	CPR MoM	EFW centile	Parity
p-value	<0.0001	*p*-value		<0.01	<0.05	NS
NPP (%)	84	Estimate	158 168	−300 601	−0,06839	0,50 961
PPP (%)	77	OR		0.049	0.93	1.66

Abbreviations: AIC, Akaike information criteria; AUC, area under the curve; CPR MoM, cerebroplacental ratio multiples of the median; DV MoM, ductus venosus pulsatility index multiples of the median; EFW, estimated fetal weight; GA at delivery, gestational age at delivery; NPP, negative predictive power; OR, odds ratio; PPP, positive predictive power.

intrapartum fetal compromise, CS-IFC)[20] or intrapartum fetal scalp pH <7.20 requiring urgent cesarean section, (2) neonatal umbilical cord pH <7.10, (3) five minute Apgar score <7 and (4) postpartum admission to neonatal unit or neonatal death. All fetuses were managed according to their progression in labor according to the hospital protocol. Of note, cases with abnormal intrapartum fetal heart rate resulting in vaginal instrumental delivery were not included as APO if fetal scalp pH or neonatal pH were within the normal limits.

2.1 | Statistical analyses

Descriptive statistics were performed evaluating maternal age, parity, GA at examination in weeks, GA at delivery in weeks, interval between ultrasound and delivery, EFW, EFW centile, cerebroplacental ratio multiples of the median (CPR MoM), ductus venosus pulsatility index multiples of the median (DV PI MoM), fetal gender, onset of labor (elective cesarean section, induction of labor and spontaneous onset of labor), mode of delivery (cesarean section for abnormal cardiotocogram, failure to progress or elective, assisted delivery and spontaneous delivery), Apgar scores at 5 min, neonatal cord arterial pH, and whether the newborn was admitted to maternity ward, neonatal ward or neonatal intensive care unit. Continuous variables are presented as median and interquartile range (IQR), while categorical variables are presented as absolute numbers and relative frequencies.

The accuracies of the CPR MoM, DV PI MoM and EFW centile for the detection of APO were evaluated using univariable logistic regression analysis, describing the estimate, odds ratio, *p*-value, receiver operating characteristic (ROC) curve with the area under the curve (AUC), Akaike information criterion (AIC), and negative and positive predictive values. However, to improve the predictive accuracy, we also applied multivariable logistic regression analysis, combining Doppler values with EFW centiles and clinical parameters (maternal age and parity) to create models in which the same statistical parameters were calculated.

To assess the validity of results and ensure consistency, additional analyses were performed adjusting with GA at delivery to rule out the effect of prematurity, while other analyses evaluated the

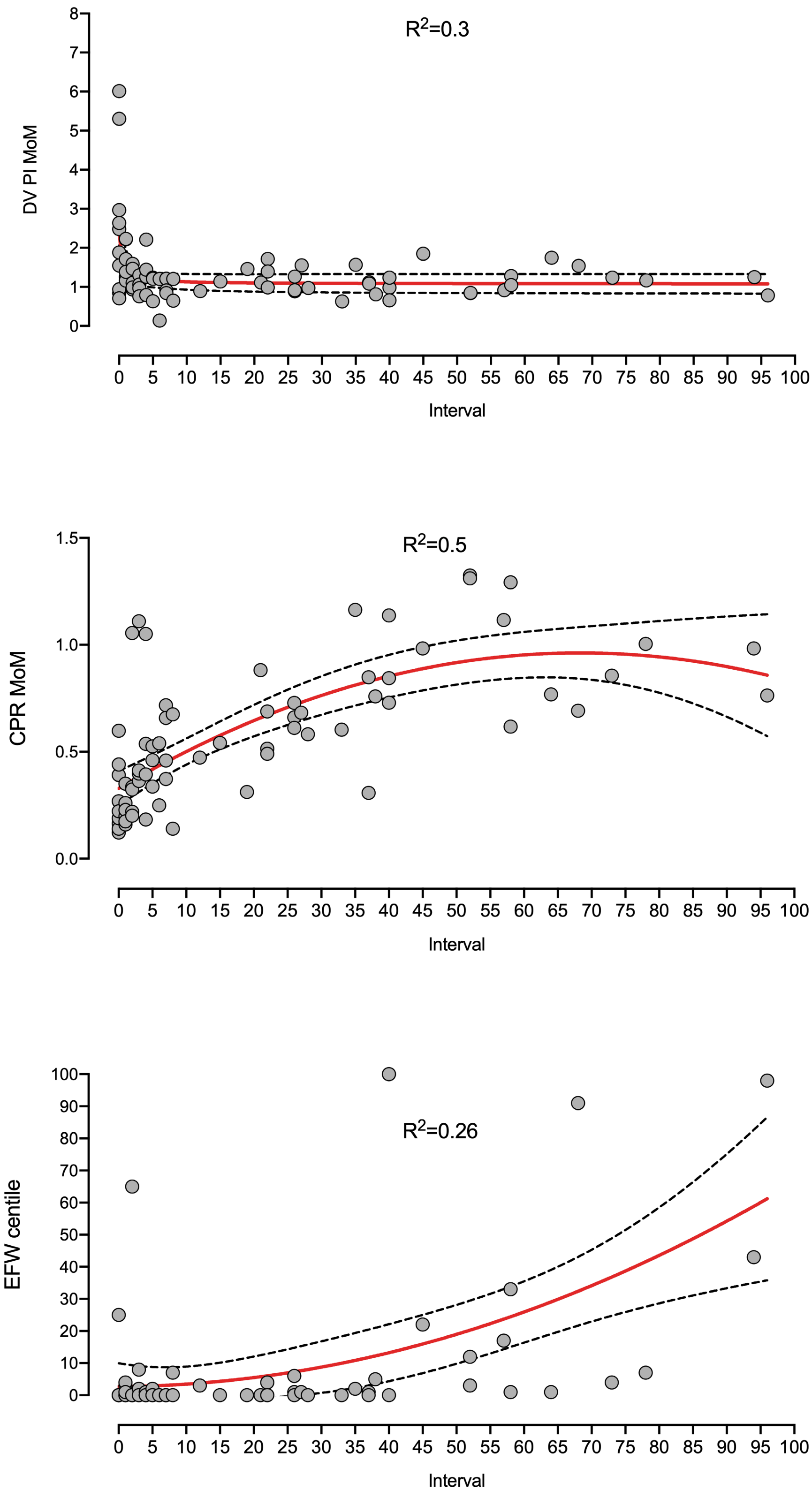

FIGURE 2 Ductus venosus (DV) pulsatility index (PI) multiples of median (MoM), cerebroplacental ratio (CPR) MoM and estimated fetal weight (EFW) centile values examined prior to 34 weeks, plotted against the interval to delivery. Interpolation curves and 95% CIs showed a moderate R^2 and suggested a chronology in the progression to abnormality. DV PI values became abnormal prior to labor (still normal values one week before birth), while progression to abnormality in case of the CPR MoM and EFW centiles started sooner and was progressively reduced (values fall from normality two and 3 months before birth).

studied parameters for the prediction of CS-IFC, in appropriate and small for gestational age (SGA) fetuses.

Comparisons were made using Mann–Whitney and Fisher's exact tests. It is important to underline that AIC was used to select the best prediction model by means of a lower AIC, which indicated the presence of a higher accuracy (a difference in the AIC of 2 units indicated significant differences and a difference of 2–4 units indicated highly significant differences).[21] There is generally a tradeoff between goodness of fit and parsimony: low parsimony models (i.e., models with many parameters) tend to have a better fit than high parsimony models. However, adding more parameters usually results in a good model fit for the data at hand, but that same model will probably be less useful in

TABLE 3 Logistic regression models for the prediction of adverse perinatal outcome prior to 34 weeks, $N=72$.

Model 1								
CPR MoM + DV PI MoM + EFW centile + maternal age + parity								
AUC (95% CI) 0.88 (0.78–0.97)								
AIC	61.6		Intercept	CPR MoM	DV PI MoM	EFW centile	Maternal age	Parity
p-value	<0.0001	*p*-value		<0.001	NS	NS	NS	NS
NPP (%)	66.7	Estimate	488 185	−503 696	0,21 585	−0,00623	−0,00391	−0,12 940
PPP (%)	88.3	OR		0.006	1.24	0.99	0.97	0.88
Model 2								
CPR MoM + DV PI MoM + EFW centile + maternal age								
AUC (95% CI) 0.88 (0.79–0.97)								
AIC	59.3		Intercept	CPR MoM	DV PI MoM	EFW centile	Maternal age	
p-value	<0.0001	*p*-value		<0.001	NS	NS	NS	
NPP (%)	66.7	Estimate	496 640	−507 991	0,20 756	−0,00608	−0,00725	
PPP (%)	88.3	OR		0.006	1.23	0.99	0.99	
Model 3								
CPR MoM + DV PI MoM + EFW centile + parity								
AUC (95% CI) 0.88 (0.79–0.97)								
AIC	59.2		Intercept	CPR MoM	DV PI MoM	EFW centile	Parity	
p-value	<0.0001	*p*-value		<0.001	NS	NS	NS	
NPP (%)	66.7	Estimate	475 573	−504 539	0,21 519	−0,00609	−0,13 400	
PPP (%)	88.3	OR		0.006	1.24	0.99	0.87	
Model 4								
CPR MoM + DV PI MoM + EFW centile								
AUC (95% CI) 0.87 (0.78–0.97)								
AIC	57		Intercept	CPR MoM	DV PI MoM	EFW centile		
p-value	<0.0001	*p*-value		<0.001	NS	NS		
NPP (%)	66.7	Estimate	472 989	−509 787	0,20 625	−0,00582		
PPP (%)	88.3	OR		0.006	1.23	0.99		
Model 5								
CPR MoM + DV PI MoM								
AUC (95% CI) 0.87 (0.78–0.96)								
AIC	55		Intercept	CPR MoM	DV PI MoM			
p-value	<0.0001	*p*-value		<0.001	NS			
NPP (%)	66.7	Estimate	476 576	−528 666	0,21 398			
PPP (%)	88.3	OR		0.0051	1.24			
Model 6								
CPR MoM + EFW centile								
AUC (95% CI) 0.88 (0.79–0.97)								
AIC	54.8		Intercept	CPR MoM	EFW centile			
p-value	<0.0001	*p*-value		<0.001	NS			
NPP (%)	66.7	Estimate	499 560	−512 469	−0,00588			
PPP (%)	88.3	OR		0.006	0.99			
Model 7								
DV PI MoM + EFW centile								
AUC (95% CI) 0.68 (0.51–0.85)								
AIC	73.7		Intercept	DV PI MoM	EFW centile			
p-value	<0.05	*p*-value		NS	<0.05			
NPP (%)	50	Estimate	0,88 690	0,58 415	−0,02291			
PPP (%)	81	OR		1.79	0.98			

TABLE 3 (Continued)

Model 8						
DV PI MoM						
AUC (95% CI) 0.56 (0.40–0.71)						
AIC	76.2		Intercept	DV PI MoM		
p-value	NS	*p*-value		NS		
NPP (%)	–	Estimate	0,53629	0,63787		
PPP (%)	79.2	OR		1.89		
Model 9						
EFW centile						
AUC (95% CI) 0.83 (0.72–0.94)						
AIC	72.7		Intercept	EFW centile		
p-value	<0.0001	*p*-value		<0.05		
NPP (%)	50	Estimate	162739	−0,02391		
PPP (%)	81	OR		0.98		
Model 10						
CPR MoM						
AUC (95% CI) 0.88 (0.79–0.97)						
AIC	52.9		Intercept	CPR MoM		
p-value	<0.0001	*p*-value		<0.0001		
NPP (%)	66.7	Estimate	503977	−531471		
PPP (%)	88.3	OR		0.0049		
Model 11						
CPR MoM + EFW centile + parity						
AUC (95% CI) 0.88 (0.79–0.97)						
AIC	57		Intercept	CPR MoM	EFW centile	Parity
p-value	<0.0001	*p*-value		<0.001	NS	NS
NPP (%)	61.5	Estimate	502893	−507038	−0,00616	−0,13068
PPP (%)	88.1	OR		0.0063	0.99	0.88

Abbreviations: AIC, Akaike information criteria; AUC, area under the curve; CPR MoM, cerebroplacental ratio multiples of the median; DV MoM, ductus venosus pulsatility index multiples of the median; EFW, estimated fetal weight; GA at delivery, gestational age at delivery; NPP, negative predictive power; OR, odds ratio; PPP, positive predictive power.

other populations. The AIC allows a good balance between parsimony and goodness of fit.[22] In addition, its purpose is not to inform about the quality of a model but to indicate in similar models the amount of lost information trying to mimic reality. This characteristic made the AIC a convenient method to compare our predictions models by selecting the model with the lowest loss of information (lowest AIC).

Statistical analysis and graphs were carried out using the Graph Pad Prism, Mac version 9.0.1, and Stat Plus Mac Pro version 8.0.1.s. Significance level was considered with a *p*-value of less than 0.05. IRB permission from the Instituto de Investigación Sanitaria La Fe (IIISLaFe) was obtained for this study (reference 2014/0063). The authors report no conflicts of interest.

2.2 | Ethics statement

Institutional Review Board permission from the Instituto de Investigación Sanitaria La Fe (IIISLaFe) was obtained for this study on April 8, 2014 (reference 2014/0063).

3 | RESULTS

Table 1 lists the characteristics of the pregnancies according to the gestational period in which they were examined. In summary, fetuses examined prior to 34 weeks' gestation had significantly longer assessment-delivery intervals ($p<0.0001$), lower EFW and birthweight centiles ($p<0.001$), more abnormal CPR MoM and DV PI MoM values ($p<0.0001$), and a higher number of APO ($p<0.0001$). In addition, they were more frequently delivered via elective cesarean section, and admitted to neonates ward ($p<0.0001$) and Neonatal Intensive Care Unit ($p<0.01$). Only 10 (13.8%) were delivered beyond 34 weeks.

Figure 1 shows the three sonographic parameters examined at or beyond 34 weeks' gestation plotted against the interval to delivery. Interpolation curves and 95% confidence intervals (CI) showed a poor R^2 and did not suggest a clear chronology of progression to abnormality.

Table 2 and Figure 3 show a comparison of different models for the prediction of APO at or beyond 34 weeks' gestation. Prediction of APO

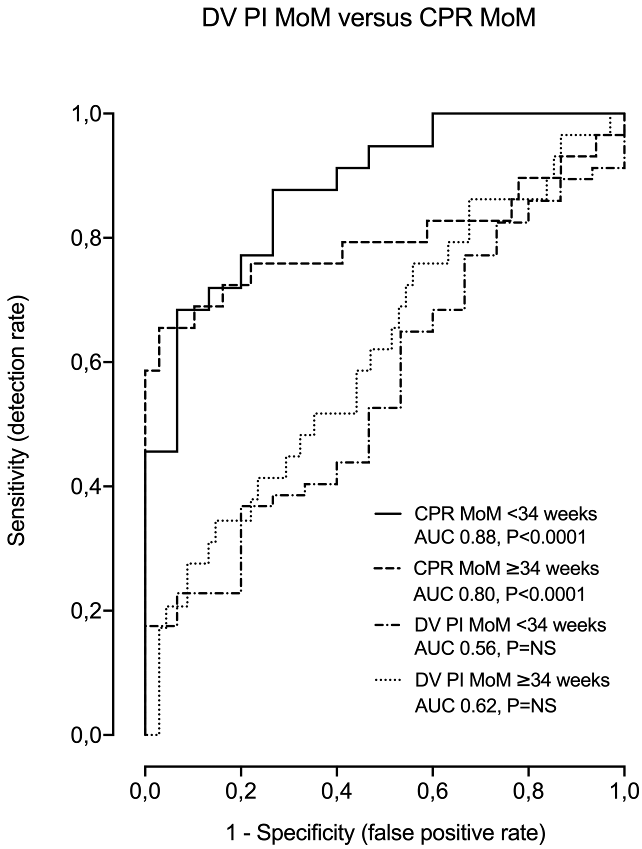

FIGURE 3 Comparison between DV PI MoM and CPR MoM for the prediction of APO at both gestational periods (<34 and ≥34 weeks).

by means of DV PI, either alone (model 8) (AUC 0.62, 95% CI: 0.49–0.74, AIC 120.6, $p>0.05$) or combined with EFW centile (model 7) (AUC 0.76, 95% CI: 0.66–0.87, AIC 113.7, $p<0.0001$) was poor. Overall, the best individual prediction model (lowest AIC) was obtained evaluating the CPR MoM, either alone (model 10) (AUC 0.80, 95% CI: 0.67–0.92, AIC 106.8, $p<0.0001$) or combined with EFW centile (Model 6: AUC 0.80, 95% CI: 0.69–0.92, AIC 103.7, $p<0.0001$). The model combining CPR MoM, EFW centile and parity (model 11) (AUC 0.81, 95% CI: 0.70–0.91, AIC 102.4, $p<0.0001$) obtained the lowest AIC of all, although AIC differences with model 6 were not significant. Finally, addition of the DV PI MoM information (models 1–5) did not improve prediction of the above-mentioned models that included CPR MoM.

Figure 2 shows the three sonographic parameters examined prior to 34 weeks' gestation plotted against the interval to delivery. Interpolation curves and 95% CIs showed a moderate R^2 and suggested a chronology in the progression to abnormality. DV PI values became abnormal prior to labor (still normal values one week before birth), while progression to abnormality in case of the CPR MoM and EFW centiles started sooner and was progressively reduced (values fell from normality two and 3 months before birth).

Table 3 and Figure 3 show a comparison of different models for the prediction of APO prior to 34 weeks' gestation. Prediction of APO by means of DV PI, alone (AUC 0.56, 95% CI: 0.40–0.71, AIC 76.2, $p>0.05$) or combined with EFW (AUC 0.68, 95% CI: 0.51–0.85, AIC 73.7, $p<0.05$) was poor. Overall, the best model (lowest AIC) was obtained using the CPR MoM alone, (model 10) (AUC 0.88, 95% CI: 0.79–0.97, AIC 52.9, $p<0.0001$) or combined with EFW centile (model 6) (AUC 0.88, 95% CI: 0.79–0.97, AIC 54.8, $p<0.0001$). In this case, parity (model 11) (AUC 0.88, 95% CI: 0.79–0.97, AIC 57, $p<0.0001$) did not improve prediction of any of both models. Finally, addition of the DV PI MoM information (models 1–5) did not improve prediction of the above-mentioned models that included CPR MoM.

To address the potential confounding effect of prematurity on APO prior to 34 weeks' gestation, we performed a secondary analysis in which we added the information of GA at delivery to the multivariable analysis (Table 4, models 12–15). The AUC and AIC notably improved (best model was model 15: AUC 0.91, 95% CI: 0.81–1.00, AIC 46.3, $p<0.0001$). Furthermore, for all models CPR MoM and GA at delivery were the only significant parameters for the prediction of APO. No significant effect was observed for the DV PI. This proved that the advantage of CPR MoM over DV PI prior to 34 weeks' gestation was not determined by prematurity.

Finally, to increase the consistency of the results, DV PI MoM and CPR MoM were compared discarding elective cesarean sections for the prediction of CS-IFC at all GAs (Table 5). Model 16 ($N=103$) studied AGA and SGA, while model 17 evaluated SGA. These models also included GA to adjust for the effect of prematurity. In fact, this effect was doubly discarded by studying CS-IFC instead of APO, as neonatal admission is frequently linked with this condition. In all cases the results persisted, and CPR remained as the only significant parameter for the prediction of CS-IFC ($p<0.01$ and $p<0.05$).

4 | DISCUSSION

According to our results, the DV PI was a poor predictor of APO before and after 34 weeks' gestation, while the best individual prediction was achieved measuring the CPR MoM. These results persisted even when considering the potential confounding effects of prematurity.

Our results were consistent with previous findings showing that early in pregnancy the DV PI tended to be the last hemodynamic parameter to become abnormal.[23–25] Conversely, in the last weeks of pregnancy, no clear chronology of progression to abnormality could be detected. Unfortunately, the progression of DV doppler anomalies according to the interval to labor has not been evaluated in the third trimester, so we did not find references to support these data.

Our results were also consistent with previous studies demonstrating the poor predictive accuracy of DV PI (AUC 0.66–0.67).[26,27] Moreover, another study[28] did not provide AUC values but described the accuracy of the DV PI as moderate (sensitivity 0.61, specificity 0.81). Interestingly, no study has compared the CPR MoM with the DV PI for the prediction of APO. However, one study has demonstrated the importance of the MCA PI/DV PI ratio in comparison with the UA PI/DV PI ratio (AUC 0.57 vs. 0.64).[29] Of note, most studies suggesting a strong relation with APO have studied extreme categorical DV abnormalities (absent or reversed a wave) because at this degree

TABLE 4 Logistic regression models for the prediction of adverse perinatal outcome prior to 34 weeks, adjusting for gestational age (GA) at delivery to address the potential confounding effect of prematurity ($N = 72$).

Model 12

CPR MoM + DV PI MoM + EFW centile + Parity + Gestational age at delivery

AUC (95% CI) 0.92 (0.83–1.00)

			Intercept	CPR MoM	DV PI MoM	EFW centile	Parity	GA at delivery
AIC	52.4							
***p*-value**	<0.0001	***p*-Value**		<0.05	NS	NS	NS	<0.01
NPP (%)	90	**Estimate**	16.82272	−4.46523	−0.02886	−0.01216	−0.01564	−0.34724
PPP (%)	90.3	**OR**		0.011	0.971	0.988	0.984	0.706

Model 13

CPR MoM + DV PI MoM + EFW centile + Gestational age at delivery

AUC (95% CI) 0.91 (0.82–1.00)

			Intercept	CPR MoM	DV PI MoM	EFW centile	GA at delivery
AIC	50						
***p*-value**	<0.0001	***p*-Value**		<0.05	NS	NS	<0.01
NPP (%)	90	**Estimate**	16.84045	−4.47772	−0.03294	−0.01211	−0.34759
PPP (%)	90.3	**OR**		0.011	0.968	0.988	0.706

Model 14

DV PI MoM + Gestational age at delivery

AUC (95% CI) 0.86 (0.72–1.00)

			Intercept	DV PI MoM	GA at delivery
AIC	56.1				
***p*-value**	<0.0001	***p*-Value**		NS	<0.001
NPP (%)	90.9	**Estimate**	18.36535	0.03008	−0.48877
PPP (%)	91.8	**OR**		1.030	0.613

Model 15

CPR MoM + Gestational age at delivery[a]

AUC (95% CI) 0.91 (0.81–1.00)

			Intercept	CPR MoM	GA at delivery
AIC	46.3				
***p*-value**	<0.0001	***p*-Value**		<0.01	<0.01
NPP (%)	81.8	**Estimate**	16.25033	−4.98471	−0.32732
PPP (%)	90.2	**OR**		0.007	0.721

Abbreviations: AIC, Akaike information criteria; AUC, area under the curve; CPR MoM, cerebroplacental ratio multiples of the median; DV MoM, Ductus venosus pulsatility index multiples of the median; EFW, estimated fetal weight; GA at delivery, gestational age at delivery; NPP, negative predictive power; OR, odds ratio; PPP, positive predictive power.

[a]This model obtained the best accuracy for the prediction of APO.

of severity the association is probably stronger.[30–32] However, some cases of fetal death occurred without preceding DV PI anomalies.[33]

Perhaps the most important study evaluating the DV PI Doppler in relation with APO was the TRUFFLE study.[34–36] However, comparisons with our study are difficult due to the different methodology, aims and conclusions: The TRUFFLE study was based on the comparison of categorical and *z*-score data according to outcome, aimed to find the best strategy to end the pregnancy to avoid long-term neurocognitive impairment, and advocated delivery according to the presence of extreme DV Doppler abnormalities, suggesting that late CPR values were not useful to influence that decision.[37] Conversely, our study applied multivariable logistic regression analysis to create prediction models that were evaluated by means of AUC and AIC, aimed to compare the predictive accuracy of DV PI and CPR MoM for APO and CS-IFC, and suggested that CPR MoM might be better than DV PI in the prediction of APO, although was not designed to conclude when to plan delivery.

According to our findings from this and previous studies,[38–40] the EFW had worse predictive accuracy than CPR MoM. This is in line with recent reports describing EFW as a poor APO determinant, especially when is taken as a standalone parameter.[41] In this regard, and despite the CPR MoM supremacy, the best prediction is probably achieved combining the information provided by both ultrasound parameters.

Previous studies have demonstrated that abnormalities in the DV PI represent the last stage of the fetal hemodynamic failure in pregnancies complicated by EO-FGR.[22–24] Moreover, these DV abnormalities tend to appear after the umbilical and middle cerebral arteries Doppler have progressively deteriorated. In this situation, it is tempting to think that the last anomaly to appear should be the one with the highest correlation with adverse outcome. However, that is

TABLE 5 Logistic regression models for the prediction of CS-IFC, adjusting for gestational age (GA) at delivery to address the potential confounding effect of prematurity. To increase the consistency of the results, DV PI MoM and CPR MoM were compared at all gestational ages discarding elective cesarean sections. Model 16 ($N=103$) included AGA and SGA, while model 17($N=74$) included SGA.

Model 16							
CPR MoM + DV PI MoM + EFW centile + Parity + Gestational age at delivery							
AUC (95% CI) 0.8558 (0.70–1.00)							
AIC	56.81		**Intercept**	**CPR MoM**	**DV PI MoM**	**EFW centile**	**GA at delivery**
***p*-value**	<0.001	***p*-Value**		<0.01	NS	NS	NS
NPP (%)	92	**Estimate**	9.898	−4.731	−0.6667	−0.01344	−0.2133
PPP (%)	50	**OR**		0.008815	0.5134	0.9867	0.8079
Model 17							
CPR MoM + DV PI MoM + EFW centile + Gestational age at delivery							
AUC (95% CI) 0.83 (0.67–1.00)							
AIC	69		**Intercept**	**CPR MoM**	**DV PI MoM**	**EFW centile**	**GA at delivery**
***p*-value**	<0.05	***p*-Value**		<0.05	NS	NS	NS
NPP (%)	88.9	**Estimate**	10.92	−4.042	−0.8083	0.008906	−0.2452
PPP (%)	50.0	**OR**		0.01756	0.4456	1.009	0.7826

Note: Model 16, $N=103$.Multivariable model for the prediction of cesarean section for intrapartum fetal compromise in AGA and SGA fetuses at 22–41 weeks. Gestational age at delivery was included to discard the effect of prematurity. Elective cesarean sections were discarded.

Model 17, $N=74$, 22–41 weeks.

Multivariable model for the prediction of cesarean section for intrapartum fetal compromise in SGA fetuses at 22–41 weeks. Gestational age at delivery was included to discard the effect of prematurity. Elective cesarean sections were discarded.

Abbreviations: AGA, appropriate for gestational age; AIC, Akaike information criteria; AUC, area under the curve; CPR MoM, cerebroplacental ratio multiples of the median; DV MoM, Ductus venosus pulsatility index multiples of the median; EFW, estimated fetal weight; GA at delivery, gestational age at delivery; NPP, negative predictive power; OR, odds ratio; PPP, positive predictive power; SGA, small for gestational age.

not necessarily true, and the association with APO might be higher in those vessels with earlier anomalies, especially if Doppler parameters are combined. Later in pregnancy, the situation differs as the hemodynamic failure pivots on cerebral vasodilation,[25] and the DV PI is usually not measured, prompting the study of the DV Doppler at this GA. Our study aimed to address these issues, clarifying the role of the DV compared to CPR MoM at different gestational periods.

Consistent with recent studies,[42] our findings showed that the predictive accuracy of DV Doppler might not be as a good as previously thought, prompting future analysis to clarify its role in the prediction of APO at early and late gestational periods. Of note, our results persisted even when the models were adjusted for GA, studied only SGA fetuses, or evaluated CS-IFC instead of APO. This proved that conclusions were consistent.

The strengths of this study included a robust statistical approach, applying continuous data and multivariable analysis, while the limitations included the fact that clinicians were not blinded to the examination, the lack of long-term follow up, the presence of occasional long examination-delivery intervals, the heterogeneity of the studied population, and the possibility of bias due to the potential confounding effect of prematurity. Some of these issues deserve a brief commentary. First, although for ethical reasons clinicians were not blinded to the examination, we tried to diminish this influence with additional analysis that discarded elective cesarean deliveries. Second, not only the DV Doppler, but also the CPR performs better with short intervals to labor.[43] Third, to adjust for the effect of prematurity, additional multivariable analyses were performed, including GA to rule out the effect of prematurity, or evaluating only CS-IFC to discard unspecific neonatal admissions. In all cases the results persisted, and CPR remained as the only significant parameter for the prediction of APO or CS-IFC.

5 | CONCLUSION

The best prediction of APO both prior to and beyond 34 weeks' gestation was achieved by means of CPR MoM evaluation. Addition of DV Doppler did not improve the predictive accuracy. However, prior to 34 weeks, it might provide useful information about fetal hemodynamic progression. Future studies are needed to determine if CPR evaluation might be useful in determining the ideal timing of delivery in pregnancies complicated by FGR.

AUTHOR CONTRIBUTIONS

José Morales-Roselló designed the study, performed the ultrasound examinations, did the statistical analysis, and wrote the manuscript. Asma Khalil supervised the final manuscript and made notable contributions to the final text. Rohan Bhate and Nashwa Eltaweel suggested valuable inputs to the text.

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interests.

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