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The fetal cerebral Doppler in the last weeks of pregnancy can select very small fetuses unlikely to present intrapartum compromise

José Morales-Roselló[a,b], Alicia Martínez-Varea[a], Blanca Novillo-Del Álamo[a] and Asma Khalil[c,d]

[a]Servicio de Obstetricia y Ginecología, Hospital Universitario y Politécnico La Fe, Valencia, Spain; [b]Departamento de Pediatría, Obstetricia y Ginecología, Universidad de Valencia, Valencia, Spain; [c]Fetal Medicine Unit, St George's Hospital, London, UK; [d]St George's University of London, London, UK

ABSTRACT

Objective: To evaluate whether, in late pregnancy, the cerebral Doppler can identify very small fetuses that are less likely to experience intrapartum compromise (IC).

Material and methods: This was a retrospective study of 282 singleton pregnancies that underwent an ultrasound scan at 32+0- 40+6 weeks and were delivered after induction, or spontaneous onset of labor. Very small fetuses were defined as fetuses with estimated weight less than the 3rd centile. IC was diagnosed in case of abnormal intrapartum fetal heart rate or intrapartum fetal scalp pH < 7.20, requiring urgent cesarean section, neonatal pH below 7.10 and Apgar score at 5 min <7. The ability of the cerebral Doppler, middle cerebral artery pulsatility index, and cerebroplacental ratio, expressed in multiples of the median (MCA PI MoM and CPR MoM), to rule out the risk of IC was evaluated alone and combined with other sonographic and clinical parameters by means of logistic regression and ROC curve analyses.

Results: The only significant parameters determining IC were parity, MCA PI, and CPR MoM. [AUC 0.62 (95% CI 0.54–0.71, $p=0.012$), 0.62 (95% CI 0.53–0.71, $p=0.008$), 0.60 (95% CI 0.51–0.69, $p=0.020$), respectively], while the best prediction was obtained combining parity with MCA PI or CPR [AUC 0.68 (95% CI 0.60–0.76), 0.67 (95% CI 0.60–0.75), $p<0.0001$ for both]. Moreover, 90% of IC cases had MCA PI and CPR values below 1.1 MoM, while 100% had MCA and CPR values below 1.5 and 1.3 MoM. Finally, the negative predictive value was 82% for any combination of parameters that included either the MCA MoM or CPR MoM.

Conclusion: The cerebral Doppler can select a group of very small fetuses that are less likely to experience IC. These fetuses might be to some extent constitutionally small and might be candidates for a more conservative and individualized management.

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Cerebroplacental ratio; middle cerebral artery; intrapartum compromise; fetal growth restriction; small for gestational age

Introduction

Late-onset fetal growth restriction (FGR) is diagnosed after 32 weeks' gestation according to the Delphi criteria in the presence of at least two of the following parameters: estimated fetal weight and abdominal circumference (EFW/AC) below the 10th centile, EFW/AC crossing >2 quartiles on growth centiles, cerebroplacental ratio (CPR) <5th centile, or umbilical artery pulsatility index (UA PI) >95th centile. Alternatively, it is diagnosed in very small fetuses, when the estimated fetal weight (EFW) or abdominal circumference (AC) are below the 3rd centile [1]. The latter scenario might be considered controversial, as the absence of hemodynamic anomalies, expected in fetuses with such poor growth might indicate that, at least, to some extent, some of them could present a very low growth potential [2] growing along the far extreme of normality.

The scale of the problem is not trivial, as all pregnancies diagnosed with late-onset FGR have been proposed to be delivered after 37 weeks [3], a procedure that aims to improve the perinatal outcome but might be deleterious in terms of iatrogenic early birth in fetuses that otherwise could potentially benefit from a more conservative approach. Moreover, some parents are reluctant to accept early induction of labor and would prefer to await the spontaneous onset of labor.

The measurement of the Doppler pulsatility index (PI), especially in the middle cerebral artery (MCA), but

CONTACT José Morales-Roselló jose.morales@uv.es Servicio de Obstetricia, Hospital Universitario y Politécnico La Fe., Avenida Fernando Abril Martorell 106, 46026, Valencia, Spain.

also in the vertebral, anterior cerebral, and posterior cerebral arteries [4–9], has proven to be a potentially useful tool to identify cerebral redistribution secondary to placental insufficiency. Furthermore, the ratios of the middle cerebral and vertebral arteries to the umbilical artery - cerebroplacental (CPR) and vertebroplacental ratios (VPR) - have emerged as a marker of fetal compromise, regardless of fetal size [10]. Therefore, the aim of this study was to evaluate whether the cerebral Doppler (MCA PI and CPR) could identify those fetuses with EFW below the 3rd centile that are unlikely to experience intrapartum compromise (IC), as these fetuses might be candidates for a more conservative and individualized approach.

Materials and methods

This was a retrospective study of 282 singleton pregnancies attending the high-risk ultrasound unit of La Fe Hospital for late-onset FGR, preeclampsia, or fetal smallness. Ultrasound assessment was performed between 32^{+0} and 40^{+6}weeks and included EFW (according to Hadlock 4 formula) and Doppler evaluation of the umbilical (UA), MCA PI, and CPR. All studied cases presented an EFW <3rd centile. However, to avoid false positive cases, only cases with an EFW < 3rd centile and a birthweight (BW) below the 3rd centile were included.

The UA and MCA were recorded using color and pulse Doppler according to standard protocols [11–12]. and the CPR was calculated as the simple ratio between the MCA PI and the UA PI [11,13]. Ultrasound assessment was performed using General Electric Voluson® (E8/E6/S8/730) ultrasound machines with 2–8 MHz convex probes, during fetal quiescence, in the absence of fetal tachycardia, and keeping the insonation angle with the examined vessels as small as possible. Only one examination per fetus (the last) was included.

Gestational age (GA) was determined according to the crown-rump length in the first trimester. To adjust for the effect of GA on fetal measurements and perform comparisons, EFW and birth weight (BW) were converted into centiles, adjusting for GA and for fetal gender using the same centile Excel calculator [14], according to the centile references of the Hospital Clinic of Barcelona. Finally, for the same purpose, MCA PI, UA PI, and CPR values were converted into multiples of the median (MoM) by dividing each value by the 50th centile (median) at each GA, as earlier described [15]. Multiple pregnancies and those complicated by major fetal abnormalities or aneuploidies were excluded. Only fetuses undergoing induction or spontaneous onset of labor were included in the study ($N=282$) as we were only interested in fetuses undergoing the stress of labor contractions. These fetuses were managed according to the progression in labor as per the local protocol [17], although the managing physicians were not blinded to the Doppler examination.

Outcome data, including birthweight, mode of delivery, Apgar score, and cord arterial pH, were collected after birth. IC was defined in cases of abnormal intrapartum fetal heart rate [18], or intrapartum fetal scalp pH [19], requiring an urgent cesarean section, or when the postnatal umbilical artery pH was <7.10. We also considered Apgar score <7 as a sign of IC. However, IC was not considered in cases of urgent instrumental delivery, provided there was a normal 5-min Apgar score and neonatal pH. Other data variables included maternal age, pre-pregnancy weight, height, body mass index, parity, and number of gestations, plus GA at examination and delivery (in weeks), interval between ultrasound assessment and birth, EFW, EFW centile, BW, BW centile, UA PI MoM, MCA PI MoM, CPR MoM, fetal gender, type of labor onset (induction and spontaneous), mode of delivery (assisted or spontaneous vaginal delivery and cesarean section due to failure to progress or IC), Apgar scores at 5 min, and neonatal cord arterial pH and baby destiny (maternal and neonatal wards or neonatal intensive care unit, NICU).

Statistical analysis

Continuous variables were presented as median and interquartile range (IQR), while categorical variables were presented as numbers and percentages.

Univariable logistic regression was used to identify the best predictors of IC using odds ratios (ORs) and ROC analysis, with the area under the curve (AUC).

The statistically significant parameters were then used in a multivariable logistic regression analysis to create prediction models that were compared according to their AUC and AIC (Akaike information criteria).

The best determinants of IC were afterwards analyzed, calculating the detection rate, (DR) for the different cutoffs. Knowing that the DR = 1-false negative rate (1-FNR) and that the FNR represents the possibility of presenting IC, we constructed graphs and tables showing the possibility of presenting IC along the different cutoffs.

Finally, as the drop in AC/EFW centiles was a key component of the Delphi criteria for defining late-onset FGR, we thought, it might be valuable to examine the drop in EFW between the 20 weeks scan and the 3rd trimester scan as an additional indicator of functional reserve. Unfortunately, we did not collect these data for all cases, so we performed this analysis in a subgroup of fetuses considering that if results were significant this would apply in a larger population. Unfortunately, we could not find accurate calculators that obtained at unison the 20 weeks and the third trimester centiles in fetuses below the 3rd centile so we decided instead to calculate for each EFW the multiples of the median (MoM) according to references earlier published by the Fetal Medicine Foundation [20] and compare the fall in MoM between vary small fetuses with normal outcome and very small fetuses with IC.

Comparisons of the continuous data variables were made using the Mann-Whitney, while the Chi Square test was used for comparing binary or categorical data variables. Statistics and graphs were performed with StatPlus® for Mac, version 7, and GraphPad Prism® for Mac, version 5. Significance was established at P values <0.05.

IRB permission was obtained for the study (Instituto de Investigación Sanatoria La Fe, reference 2014/0063). Patient consent was not required as this study was based on publicly available data. The authors report no conflicts of interest.

Results

Figure 1 shows how the fetuses were selected according to the mode of delivery. Despite the managing physician usually considered elective cesarean or labor induction, in a proportion of cases, labor started spontaneously, either because management was initially conservative, because labor started spontaneously before delivery was scheduled or because the patient rejected induction in favor of a low-intervention birth.

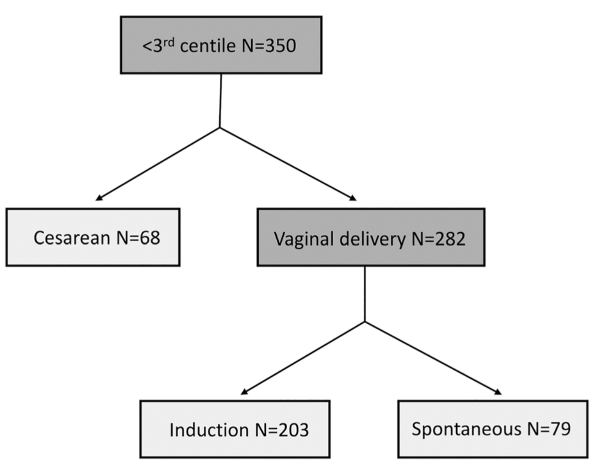


Figure 1. Flow diagram describing the selection of the study population.

Of the 350 cases with BW <3rd centile, 68 were finished with elective cesarean sections, while 282 underwent induction ($N=203$) or spontaneous onset of labor ($N=79$). Only the last cases (induction or spontaneous onset of labor) were included in the study.

The study population is described in Table 1. In summary, most fetuses were male (52.5%) and were delivered after induction (72%). Spontaneous vaginal delivery occurred in 50% of cases, 14.2% of fetuses had an abnormal intrapartum fetal heart rate or scalp pH below 7.20, requiring an emergency cesarean section, and 3.9% and 1.4% presented cord blood arterial pH values below 7.10 and a 5-min Apgar score below 7, respectively. When pregnancies presenting IC and normal pregnancies were compared, the former were more frequently nulliparous, presented a lower parity, had lower MCA PI MoM and CPR MoM values, and were more frequently admitted to the neonatal ward.

Table 2 and Figure 2 show the logistic regression analysis and ROC curves for the prediction of IC. Only parity, MCA PI, and CPR MoM were significant determinants [AUC 0.62 (95% CI 0.54–0.71, $p=0.012$), 0.62 (95% CI 0.53–0.71, $p=0.008$), and 0.60 (95% CI 0.51–0.69, $p=0.020$), respectively], while the best prediction was obtained combining parity with MCA PI or CPR [AUC 0.68 (95% CI 0.60–0.76), 0.67 (95% CI 0.60–0.75), $p<0.0001$ for both].

Figure 3 shows the possibility of IC, according to the CPR MoM and MCA PI MoM values. For CPR values beyond 1 MoM, 1.1 MoM, and 1.3 MoM, the possibility of IC was respectively 20%, 10%, and 0%. For MCA PI values beyond 1 MoM, 1.1 MoM, and 1.5 MoM, the possibility of IC was respectively 25%, 10%, and 0%. In addition, according to the logistic regression analysis, the negative predictive value was 82% using any combination of parameters that included either the MCA MoM or CPR MoM.

Finally, Tables 3 and 4 show the MCA PI and CPR references at 32–42 weeks, corresponding to the different thresholds for intrapartum compromise (IC) depicted in Figure 3. The medians or 50th centiles were characterized by the following equations:

$$\mathrm{MCAPIMedian} = -3.266164164 + 0.368135209 * \mathrm{GA} - 0.006318278 * \mathrm{GA}^2.$$

$$\mathrm{CPRMedian} = -2{,}799017859 + 0{,}28314081 * \mathrm{GA} - 0{,}004341202 * \mathrm{GA}^2.$$

Where GA was the gestational age expressed in weeks with decimals.

This meant that considering absolute values, the possibility of IC at 39 weeks for fetuses with CPR values

Table 1. Descriptive analysis of the study population ($N = 282$).

	All pregnancies ($N = 282$) Mean (SD); Median (1st, 3rd quartile)	No intrapartum compromise ($N = 232$) Mean (SD); Median (1st, 3rd quartile)	Intrapartum compromise ($N = 50$) Mean (SD); Median (1st, 3rd quartile)	2 vs 3* P-value
Maternal age in years	31.9 (5.5); 32 (28, 36)	31.8 (5.5); 32 (28,36)	32 (6); 32 (28.7, 36)	0.785
Maternal pre-pregnancy weight (kgs)	59.8 (11.8); 59 (51.7, 67)	59.4 (11.8); 58 (51, 67)	62.2 (11.5); 63 (55, 69)	0.196
Maternal height (cm)	161.6 (6.5); 162 (158, 166)	161.5 (6.4); 162 (158,165.3)	162.3 (7.2);162 (158, 168)	0.652
Maternal Body Mass Index, Kg/m2	22.7 (4.4); 22 (19.5, 25)	22.6 (4.4); 22 (19,25)	23.65 (4.8); 23 (21, 27)	0.249
Gestational age at examination (weeks)	37.9 (2.02); 38.3 (37, 39.4)	37.9 (2); 38.14 (37,39.4)	37.8 (2.2); 38.6 (36.7, 39.6)	0.905
Gestational age at delivery (weeks)	39 (1.68); 39.4 (37.8, 40.3)	39.1 (1.6); 39.4 (37.9,40.3)	38.8 (2); 39.4 (37.6, 40.3)	0.627
Estimated fetal weight in grams	2361 (481); 2412 (2075, 2667)	2370 (483); 2405 (2087, 2670)	2318 (473); 2461 (1973, 2665)	0.874
Estimated fetal weight centile	6.4 (12.5); 2 (0, 7)	6.8 (13.3); 2 (0,7)	4.7 (7.7); 2 (0, 6)	0.847
UA PI MoM	1.28 (0.28); 1.25 (1.06, 1.46)	1.27 (0.26); 1.26 (1.05,1.46)	1.33 (0.32); 1.2 (1.1, 1.5)	0.300
MCA PI MoM	0.90 (0.22); 0.87 (0.74, 1.06)	0.92 (0.21); 0.89 (0.76, 1.07)	0.84 (0.23); 0.80 (0.68, 0.98)	0.008
CPR MoM	0.82 (0.28); 0.78 (0.61, 0.99)	0.84 (0.28);0.81 (0.63, 0.99)	0.73 (0.27); 0.70 (0.53, 0.95)	0.020
Interval examination-delivery (days)	8.1 (8.6); 6 (2, 11)	8.2 (8.8); 6 (2,11)	7.3 (7.9); 5 (2, 8.2)	0.395
Birth weight in grams	2340 (315); 2410 (2134, 2580)	2348 (313); 2405 (2140, 2598)	2305 (327); 2438 (2015, 2563)	0.467
Birth weight centile	1 (0.79); 1 (0, 2)	1 (0.81); 1 (0,2)	0.9 (0.72); 2 (0, 1)	0.792
	N (%)	N (%)	N (%)	
Nulliparity	143 (50.7)	130 (56)	40 (80)	0.001
Preterm birth (<37 weeks)	28 (9.9)	21 (9)	7 (14)	0.299
Male sex	148 (52.5)	120 (51.7)	28 (56)	0.641
Type of labor onset				
Induction of labor	203 (72)	162 (69.8)	41 (82)	0.086
Spontaneous onset of labor	79 (28)	70 (30.2)	9 (18)	0.086
Apgar <7 at 5 min	4 (1.4)	0 (0)	4 (8)	<0.001
Arterial pH <7.10	11 (3.9)	0 (0)	11 (22)	<0.0001
Mode of birth				
Cesarean section (failure to progress)	35 (12.4)	34 (14.6)	1 (2)	0.009
Cesarean section (abnormal CTG)	40 (14.2)	0 (0)	40 (80)	<0.0001
Assisted vaginal delivery	67 (23.7)	63 (27)	4 (8)	0.003
Spontaneous vaginal delivery	140 (49.6)	135 (58.2)	5 (10)	<0.0001
Neonatal transfer				
Maternal ward	218 (77.3)	187 (80.6)	31 (62)	0.008
Neonatal ward	63 (22.3)	45 (19.4)	18 (36)	0.015
Neonatal Intensive care unit (NICU)	0 (0)	0 (0)	0 (0)	1
NICU + subsequent postnatal death	1 (0.35)	0 (0)	1 (2)	0.177

*Mann-Whitney U test.
UA PI MoM, umbilical artery pulsatility index multiples of the median; MCA PI, middle cerebral artery pulsatility index multiples of the median; CPR, cerebroplacental ratio; CTG, cardiotocogram (fetal monitoring); SD, standard deviation.

Table 2. Logistic regression analysis for the prediction of intrapartum compromise in fetuses with birth weight <3rd centile.

	OR (95% CI)	P-Value	AUC (95% CI)	P-Value
Univariable analysis				
MCA PI MoM	0,17 (0.04, 0.78)	0.023	0.62 (0.53, 0.71)	0.008
UA PI MoM	2.41 (0.81, 7.12)	0.112	0.55 (0.46, 0.64)	0.299
CPR MoM	0.23 (0.07, 0.78)	0.019	0.60 (0.51, 0.69)	0.020
EFW centile	0.98 (0.95, 1.02)	0.295	0.51 (0.42, 0.59)	0.900
Maternal age	1.00 (0.95, 1.06)	0.858	0.51 (0.42, 0.60)	0.784
Maternal pre-pregnancy weight	1.02 (0,98, 1.06)	0.297	0.58 (0.46, 0.71)	0.194
Maternal height	1.02 (0.95, 1.09)	0.593	0.53 (0.39, 0.67)	0.649
Parity	0.44 (0.23, 0.83)	0.005	0.62 (0.54, 0.71)	0.012
Fetal sex	1.19 (0.64, 2.20)	0.583	0.52 (0.43, 0.61)	0.635
GA at examination	0.97 (0.84, 1.13)	0.734	0.50 (0.41, 0.59)	0.904
Multivariable analysis				
CPR MoM + Parity				
CPR MoM	0.25 (0.07, 0.85)	0.027	0.67 (0.60, 0.75)	<0.0001
Parity	0.43 (0.23, 0.78)	0.006		
Model: −0.11138 − 0.84975 * Parity −1.40161*CPR MoM, AIC 253.9				
MCA PI MoM + Parity				
MCA PI MoM	0.18 (0.04, 0.89)	0.035	0.68 (0.60, 0.76)	<0.0001
Parity	0.43 (0.23, 0.79)	0.006		
Model: 0.26838 − 0.84755 * Parity −1.68402*MCA MoM, AIC 254.4				

MCA, Middle cerebral artery; UA, umbilical artery; CPR, cerebroplacental ratio; MoM, multiples of the median; AIC, Akaike Information Criteria.

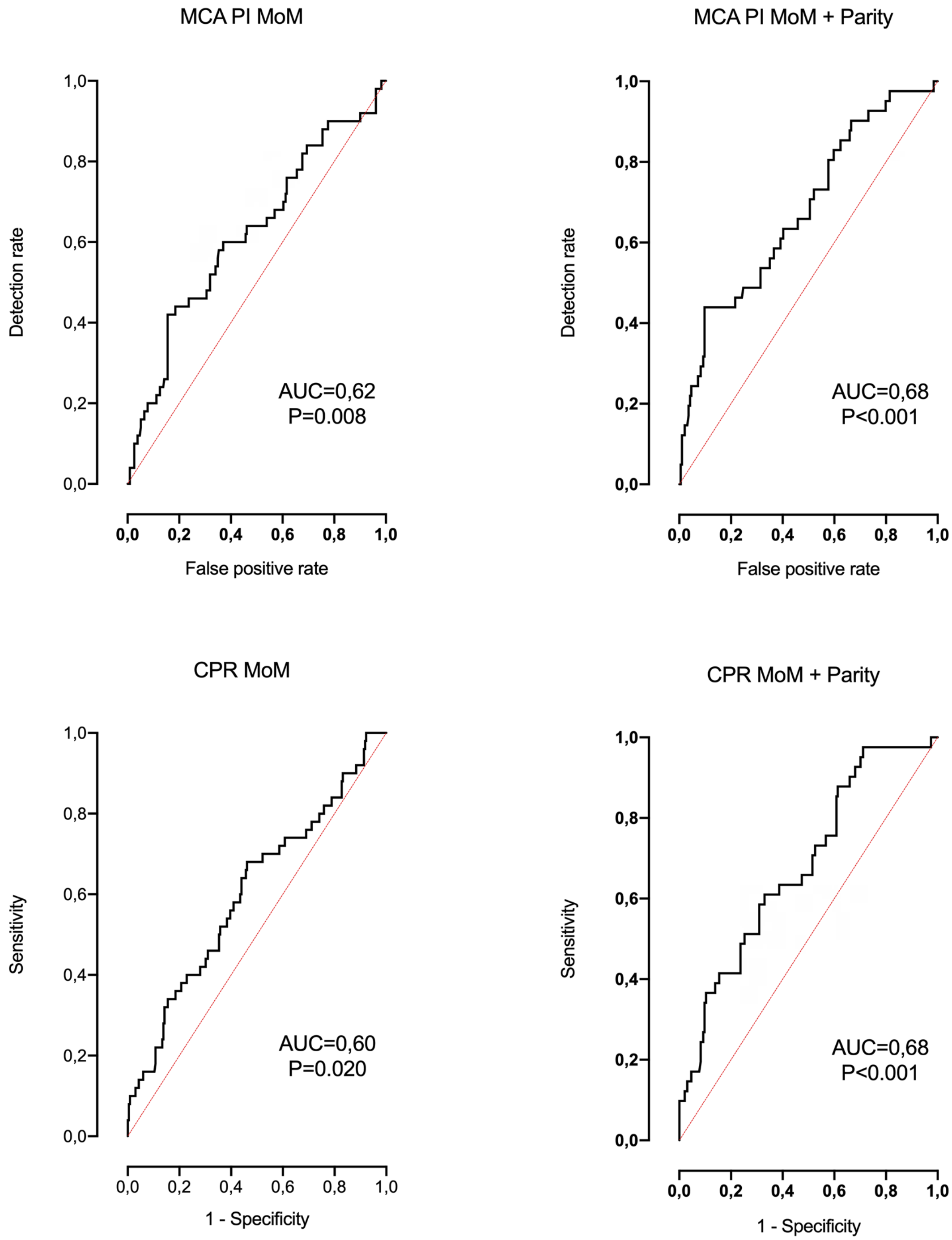


Figure 2. ROC curves showing the accuracy of the MCA PI MoM, CPR MoM, MCA PI MoM plus parity, and CPR MoM plus parity for the prediction of intrapartum compromise in fetuses with birthweight below the 3rd centile.

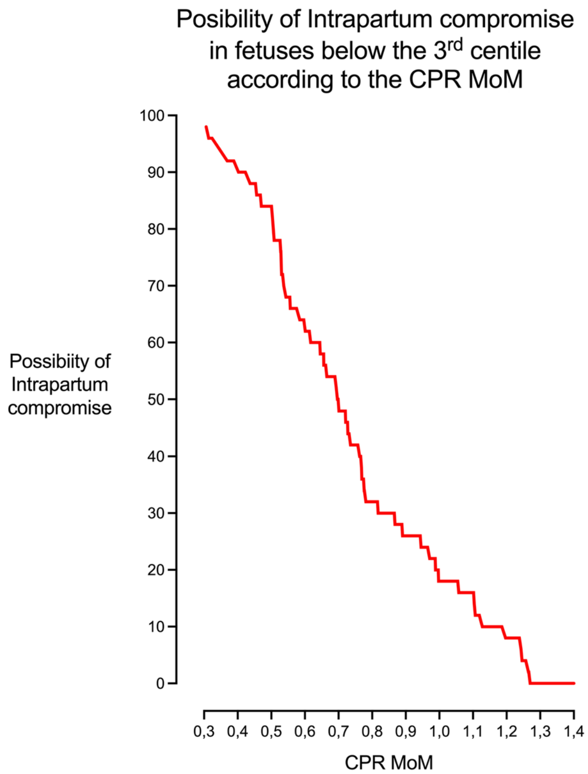
over 2.13, 1.80, and 1.64 would be respectively 0%, 10%, and 25%, while the possibility of IC at 39 weeks for fetuses with MCA PI values over 2.22, 1.63, and 1.48 would be respectively 0%, 10%, and 25%.

Finally, Figure 4 compares the fall in EFW (expressed in MoM) between very small fetuses with normal outcome and very small fetuses with IC. Although due to the low number of normal and IC cases ($N=53$ and $N=8$), the results were not significant, very small fetuses with IC presented a higher reduction of EFW between the second and third trimester, supporting the existence of a poorer functional reserve in line with the Delphi definition of late-onset FGR.

Discussion

Summary of key findings

Among very small fetuses at the end of pregnancy, cerebral Doppler can select those that are less likely



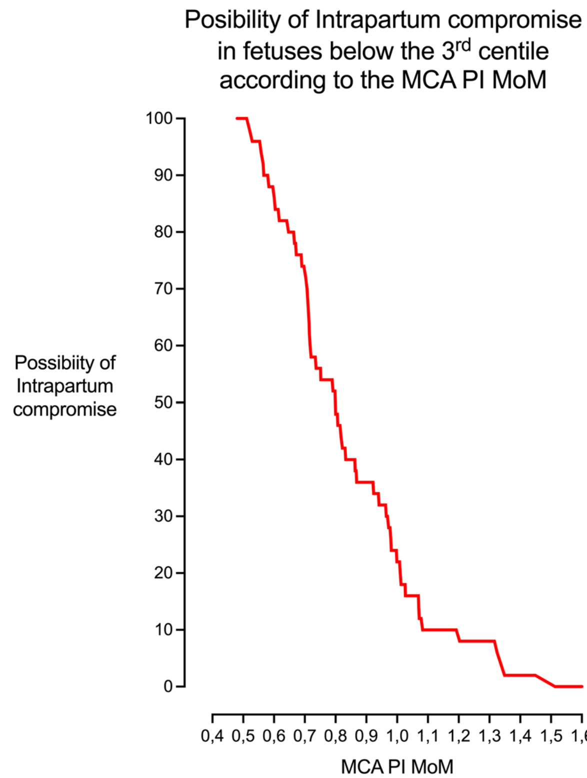


Figure 3. Possibility of intrapartum compromise according to the values of the MCA PI MoM, and CPR MoM. For CPR values beyond 1 MoM, 1.1 MoM, and 1.3 MoM, the possibility of intrapartum compromise was respectively 20%, 10%, and 0%. for MCA PI values beyond 1 MoM, 1.1 MoM, and 1.5 MoM, the possibility of an intrapartum compromise was respectively 25%, 10%, and 0%. according to the logistic regression analysis, the negative predictive value was 82% using any combination of parameters that included either the MCA MoM or CPR MoM.

Table 3. Middle cerebral artery (MCA) pulsatility index (PI) references at 32–42 weeks corresponding to the different MoM values shown in Figure 3.

Gestational week	1 MoM Possibility of IC 25%	1.1 MoM Possibility of IC 10%	1.5 MoM Possibility of IC 0%
32	2.04	2.24	3.06
33	2.00	2.20	3.00
34	1.95	2.14	2.92
35	1.88	2.07	2.82
36	1.80	1.98	2.70
37	1.71	1.88	2.56
38	1.60	1.76	2.40
39	1.48	1.63	2.22
40	1.35	1.48	2.02
41	1.21	1.33	1.81
42	1.05	1.15	1.57

Median (1 MoM) = −3.266164164 + 0.368135209 * GA − 0.006318278 * GA^2.
Where GA was gestational age in weeks plus decimals.
The possibility of intrapartum compromise (IC) for fetuses with MCA PI values beyond 1, 1.1, and 1.5 MoM was respectively 25%, 10%, and 0%.
According to the table, the possibility of IC at 39 weeks for fetuses with MCA PI values over 1.48, 1.63, and 2.22, would be respectively 25%, 10%, and 0%.

Table 4. Cerebroplacental ratio (CPR) references at 32–42 weeks corresponding to the different MoM values shown in Figure 3.

Gestational week	1 MoM Possibility of IC 20%	1.1 MoM Possibility of IC 10%	1.3 MoM Possibility of IC 0%
32	1.82	2.00	2.37
33	1.82	2.00	2.37
34	1.81	1.99	2.35
35	1.79	1.97	2.33
36	1.77	1.95	2.30
37	1.73	1.90	2.25
38	1.69	1.86	2.20
39	1.64	1.80	2.13
40	1.58	1.74	2.05
41	1.51	1.66	1.96
42	1.44	1.58	1.87

Median (1 MoM) = − 2.799017859 + 0.28314081 * GA − 0.004341202 * GA^2.
Where GA was gestational age in weeks plus decimals.
The possibility of intrapartum compromise (IC) for fetuses with CPR values beyond 1, 1.1, and 1.3 MoM was respectively 20%, 10%, and 0%.
According to this table, the possibility of IC at 39 weeks for fetuses with CPR values over 1.64, 1.80, and 2.13 would be respectively 20%, 10%, and 0%.

to present IC. These fetuses, especially in non-nulliparous mothers, might be suitable for a more conservative approach. Considering only the cerebral Doppler, for MCA PI values beyond 1 MoM, 1.1 MoM, and 1.5 MoM, the possibility of IC would be only 25%, 10%, and 0%, while for CPR values beyond 1 MoM, 1.1 MoM, and 1.3 MoM, this possibility would be 20%, 10%, and 0%.

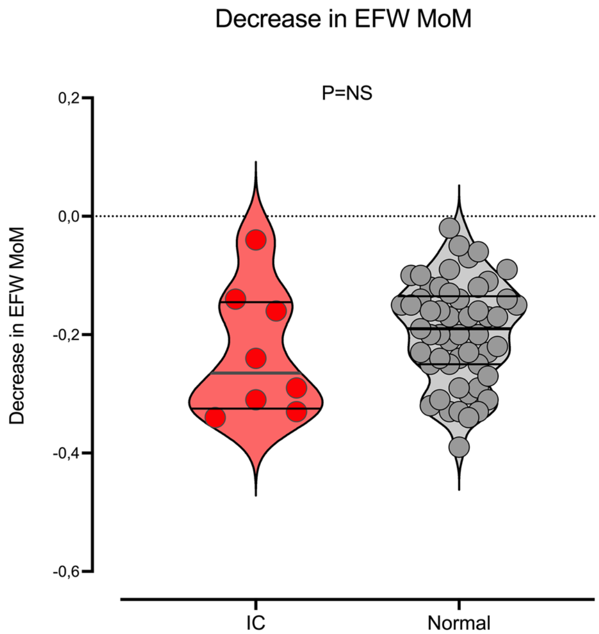


Figure 4. Fall in EFW expressed in multiples of the median (MoM) between very small fetuses with normal outcome and very small fetuses with IC.

Interpretation of study findings and comparison with published literature

Current consensus accepts that some of the fetuses below the 10th centile (those with normal Doppler) are genetically small. However, a different yardstick is applied in the case of fetuses below the 3rd centile, in whom extreme smallness is considered sufficient for the diagnosis of fetal growth restriction [21]. Our work proves that in this group of fetuses, those with a higher cerebral impedance are less likely to present IC, and therefore, similarly to the fetuses below the 10th centile, might be genetically small.

Our results are in line with earlier reports suggesting that EFW centiles are poor predictors of adverse outcomes in fetuses growing below the 3rd centile [22] and with publications suggesting a similar poor inaccuracy for the UA PI, which does not correlate with the existence of pathological lesions causing suboptimal placental function [23,24]. Moreover, they support the growing literature in favor of cerebral flow as a method to select compromised fetuses independently of fetal weight [15,16]. In this regard, the reduction of the cerebral flow impedance would reflect the imbalance between fetal demands and suboptimal placental supply, which in fetuses less likely to develop IC and more prone to low genetic potential would remain unchanged despite the apparent notorious smallness.

Research and clinical implications

If cerebral Doppler can select fetuses below the 3rd centile that are less likely to present IC, this would suggest that even among the very small fetuses [5], not all present the same functional reserve. Genetic smallness would behave as a continuum, decreasing its proportion as we approach the lowest limits of the population chart. In this regard, fetuses that are less likely to develop IC would have a higher probability of being genetically small and, especially in non-nulliparous women, might be managed with a more conservative approach.

Finally, these findings are in line with the existence of a higher fall in the median EFW observed in fetuses with IC, which is in line with the Delphi definition of FGR and the rationale of a poorer functional reserve in this subgroup of small fetuses.

The strengths of the study are its novelty, as this is the first study to evaluate with cerebral Doppler (MCA PI and CPR), the existence of genetic smallness in fetuses growing below the 3rd centile, and the accurate statistical methodology using logistic regression analysis combined with ROC curves. Conversely, limitations include the retrospective nature of the study, the absence of other parameters such as the uterine Doppler or the growth velocity, and the possibility of intervention bias as the managing physicians were not blinded to the Doppler examination results.

In conclusion, the MCA PI MoM and CPR MoM can select very small fetuses that are less likely to present IC. A number of these fetuses might be to some extent genetically small, representing the extreme of constitutional smallness, and might be, especially in multiparous women, candidates for a more conservative approach. More studies are needed to corroborate this hypothesis.

Ethical approval

IRB permission was obtained for the study (Instituto de Investigación Sanatoria La Fe, reference 2014/0063).

Author contributions

José Morales-Roselló contributed with the conceptualization, data curation, analysis, writing of the original draft, supervision, and review. Alicia Martínez-Varea, Blanca Novillo-Del Álamo, and Asma Khalil contributed with its supervision, and review.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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ORCID

José Morales-Roselló http://orcid.org/0000-0002-8783-6710
Alicia Martínez-Varea http://orcid.org/0000-0002-7600-4281

Data availability statement

Data is available on request from the author.

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