

ORIGINAL ARTICLE



Is it possible to predict late antepartum stillbirth by means of cerebroplacental ratio and maternal characteristics?

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ABSTRACT

Objective: To examine the potential value of fetal ultrasound and maternal characteristics in the prediction of antepartum stillbirth after 32 weeks' gestation.

Methods: This was a retrospective multicenter study in Spain. In 29 pregnancies, umbilical artery pulsatility index (UA PI), middle cerebral artery pulsatility index (MCA PI), cerebroplacental ratio (CPR), estimated fetal weight (EFW), and maternal characteristics were recorded within 15 days prior to a stillbirth. The values of UA PI, MCA PI, and CPR were converted into multiples of the normal median (MoM) for gestational age and the EFW was expressed as percentile according to a Spanish reference range for gestational age. Data from the 29 pregnancies with stillbirths and 2298 control pregnancies resulting in livebirths were compared and multivariate logistic regression analysis was used to determine significant predictors of stillbirth.

Results: The only significant predictor of stillbirth was CPR (OR = 0.161, 95% confidence interval [CI] 0.035, 0.654; $p = .014$); the area under the receiver operating characteristics curve was 0.663 (95% CI 0.545, 0.782) and the detection rate (DR) was 32.14% at a 10% false-positive rate (FPR). In addition, when we included MCA and UA PI MoM instead of CPR, only MCA PI MoM was significant (OR = 0.104, 95% confidence interval [CI] 0.013, 0.735; $p = .029$), with similar prediction abilities (area under the curve (AUC) 0.645, DR 28.6%, FPR 10%).

Conclusions: The CPR and MCA PI are predictors of late stillbirth but the performance of prediction is poor.

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Cerebroplacental ratio; fetal growth restriction; fetal hemodynamics; fetal middle cerebral artery Doppler; stillbirth; umbilical artery Doppler

Introduction

Antepartum stillbirth is reported in 2–4/1000 pregnancies in developed countries and is 10 times higher in the underdeveloped countries [1]. In most stillbirths at <32 weeks' gestation, the fetuses are small for gestational age (SGA) and there is evidence of impaired placentation [2,3]. In contrast, in most stillbirths after 32 weeks' gestation, the fetuses are appropriately grown for gestational age (AGA) [4,5]. Some of the AGA stillbirths are associated with abnormalities in fetal Doppler indices, especially in the cerebroplacental ratio (CPR). As the CPR reflexes, the unbalance

between fetal needs and placental supply, which characterizes the physiopathology of late-onset fetal growth restriction (FGR), abnormal CPR values would suggest the existence of failure to reach the growth potential (FRGP) [6,7] (fetal growth under optimal conditions). However, despite FRGP, fetuses with abnormal CPR have been proven to be at risk of intrapartum compromise [8–12], the relationship between these hemodynamic disturbances and fetal death has not been yet established.

The objectives of this study is to report fetal Doppler indices obtained within 2 weeks of

antepartum stillbirth and develop a model for prediction of such stillbirths from fetal Doppler indices, estimated fetal weight, and maternal characteristics.

Materials and methods

This was a retrospective multicenter case control study in four university hospitals in Spain. In 29 pregnancies, umbilical artery pulsatility index (UA PI), middle cerebral artery pulsatility index (MCA PI), CPR, estimated fetal weight (EFW), and maternal characteristics were recorded within 15 days prior to antepartum stillbirth. Every stillborn fetus was matched with 80 liveborn fetuses. The 2298 control cases were collected from the same participating hospitals and were randomly selected among the routinely evaluated population at 32–34, 35–37, 38–40, and 40–41 weeks' gestation. For each case and control, gestational age was determined from the crown-rump length in the first trimester. Pregnancies complicated by fetal abnormalities or aneuploidies were excluded even when these were found after delivery or in postmortem studies.

The UA PI and MCA PI were evaluated using color Doppler according to standard protocols [13,14] and the CPR was calculated as the ratio between the MCA PI and the UA PI [15].

EFW was obtained from fetal biometry using the Hadlock-4 equation [16]. The values of UA PI, MCA PI, and CPR were converted into multiples of the normal median (MoM) for gestational age by dividing the observed values by the 50th percentile at each gestational age according to the previously published reference ranges: [14,17]

$$\text{UA PI 50th percentile} = 2.2037 - 0.057955 \times \text{GA} + 0.00053953 \times \text{GA}^2$$

$$\text{MCA PI 50th percentile} = -3.266164164 + 0.368135209 \times \text{GA} - 0.006318278 \times \text{GA}^2$$

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

Where GA is the gestational age expressed in weeks including decimals.

The EFW was expressed as percentile according to a Spanish reference range for gestational age [18].

Statistical analysis

Descriptive statistics were performed evaluating maternal age, racial origin (Caucasian and nonCaucasian), height and weight (expressed as body mass index, BMI), EFW, birth weight (BW), gravidity

(defined as the total number of pregnancies including the current pregnancy and all previous miscarriages), parity (defined as the total number of previous vaginal deliveries and cesarean sections after 24 weeks' gestation), fetal sex, GA at examination, GA at delivery, the interval between examination and delivery, mode of delivery (spontaneous vaginal delivery, instrumental delivery and emergency or elective cesarean section) and Apgar score at 5 min. Median and interquartile range (IQR) were calculated for continuous variables and absolute and relative frequencies were calculated for categorical variables. Comparisons between stillbirths and controls were performed with the chi-square test in the case of categorical variables and the Mann-Whitney *U* test was carried out in the case of continuous variables.

Multivariate logistic regression analysis was used to determine significant predictors of stillbirth. In these models, the MCA and UA PI MoM were evaluated individually and also in the form of CPR MoM in order to assess the relative importance of each parameter. The Akaike information criterion (AIC) was used to select the best prediction model (the most parsimonious combination) by means of a lower AIC, which indicated the presence of higher accuracy (a difference in the AIC of two units indicated significant differences and a difference of 2–4 units indicated highly significant differences). There is generally a trade-off 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. This is not usually a good approach, adding more parameters usually results in a good model fit for the data at hand, but that same model will likely be useless for predicting other data sets. The AIC allows a good balance between parsimony and goodness of fit. The results of the logistic regression were reported in the form of odds ratios (OR) with their 95% confident interval (CI) and *p* values. Detection rates (DR) for a false-positive rate (FPR) of 5 and 10% and ROC analysis with the area under the curve (AUC) were used to evaluate the ability of the model to predict stillbirth. Statistical analysis and graphs were performed using R-Software® 3.4.3 (<http://www.r-project.org/>). Statistical significance was established at *p* < .05. The authors report no conflict of interests.

Results

Maternal and pregnancy characteristics in the stillbirths and controls are compared in Table 1. In the stillbirths, compared to livebirths, there was a higher

Table 1. Comparison between the livebirth and stillbirth groups.

Variable	Livebirth (N = 2298) Median (IQR)	Stillbirth (N = 29) Median (IQR)	p-value
Continuous data			
BMI (kg/m ²)	23.8 (21.5, 27.2)	23.5 (21.4, 25.5)	.403
GA at examination (weeks)	36.43 (34.14, 38.43)	35.6 (34, 37.3)	.278
EFW (Hadlock-4) (g)	2724 (2266, 3149)	2527 (2169, 2859)	.099
EFW centile ^a	50 (41, 61)	44 (8, 81)	.279
Age (years)	33 (29, 36)	31 (28, 36)	.374
Parity	0 (0, 1)	0 (0, 1)	.942
UA PI MoM	1.08 (0.95, 1.24)	1 (0.89, 1.27)	.334
MCA PI MoM	0.94 (0.82, 1.09)	0.86 (0.68, 1.05)	.032
CPR MoM	1.05 (0.87, 1.26)	0.97 (0.68, 1.19)	.055
GA at delivery (weeks)	40 (39, 40.71)	37.14 (34.86, 38.71)	<.0001
Interval (days)	20 (7, 38)	9 (5, 10)	<.0001
BW(g)	3250 (3000, 3504)	2700 (2180, 3240)	<.0001
BW centile ^a	40 (20, 62)	35 (4, 74)	.955
Apgar 5 min	10 (10, 10)	0 (0, 0)	<.0001
Variable	N (%)	N (%)	p-Value
Contingency data			
SGA (BW < P10 ^b)	256 (11.14)	8 (27.59)	.013
CPR MoM <0.6765 ^b	148 (6.4)	8 (27.6)	<.0001
Nulliparity	1150 (50.0)	15 (51.7)	.857
Apgar 5 min <7	3 (0.13)	29 (100)	<.0001
Delivery via			
Assisted VD.	464 (20.19)	2 (6.9)	.191
Cesarean S.	487 (21.19)	8 (27.59)	
Nonassisted VD.	1347 (58.62)	19 (65.52)	
Fetal gender			
Female	1103 (48)	12 (41.38)	.602
Male	1195 (52)	17 (58.62)	
Ethnicity			
Caucasian	2266 (98.61)	25 (86.21)	p <.0001
Noncaucasian	32 (1.39)	4 (13.8)	

IQR: interquartile range; BMI: body mass index; SGA: small for gestational age; GA: gestational age; EFW: estimated fetal weight; BW: birth weight; ^aaccording to Hospital Clinic de Barcelona references; ^bCPR MoM values below 0.6765 suggest the presence of failure to reach the growth potential; UA: umbilical artery; MCA: middle cerebral artery; CPR: cerebroplacental ratio; PI: pulsatility index; MoM: multiples of the median; interval: difference between GA at examination and delivery.

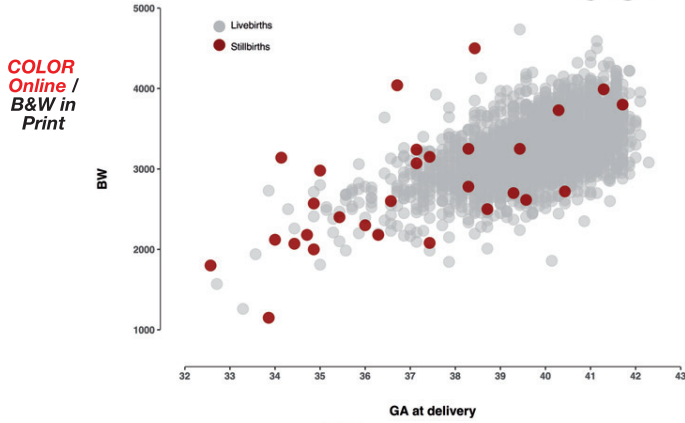


Figure 1. Birthweight in stillbirths (red circles) and livebirths (gray circles) according to gestational age. Stillbirths are situated throughout the entire spectrum of the BW distribution.

incidence of non-Caucasian maternal racial origin, lower MCA PI MoM, lower gestational age at birth, shorter examination to delivery interval, lower median BW and incidence of BW <10th percentile. The BW in the stillbirths and controls are plotted in [Figure 1](#). The BW was <10th percentile in 27.6% (8 of 29) stillbirths and in 11.1% (256 of 2298) livebirths.

In the group of stillbirths, 21 (72.4%) pregnancies had at least one risk factor: 8 (27.6%) were SGA, 2 (6.9%) had anomalies of the placental insertion (marginal placenta and placenta previa), 5 (17.2%) had hypertension (1 gestational hypertension and 4 preeclampsia), 3 (10.3%) had diabetes mellitus (1 pregestational and 2 gestational), 4 (13.8%) had thrombophilia (1 antithrombin III deficit, 1 factor V Leyden, 1 protein S deficit, and 1 unspecified) and 1 (3.4%) had unexplained antepartum hemorrhage from 29 weeks' gestation. However, in 8 cases (27.6%), no risk factor was observed, either before or after the baby was born and fetal death was diagnosed during a routine ultrasound examination or after emergency consultation for lack of fetal movements. Regarding the existence of immediate causes of death, detected after consultation, abruption was present in 6 (20.7%) cases. In addition, cord anomalies were seen in three fetuses (10.3%) (1 velamentous insertion and 2 cord loop compression).

In the multiple regression analysis, the only significant predictor of stillbirth was CPR MoM ([Table 2](#)) with an AUC of 0.663 ([Figure 2](#) left). Interestingly,

Table 2. Model for term stillbirth prediction using CPR.

EFW according to local references						
Variables	Estimate	Std. Error	OR	Lower 95%	Upper 95%	p-value
(Intercept)	2.787	3.095	16.236	0.039	7673.084	.368
Age	-0.033	0.035	0.968	0.905	1.038	.348
BMI	-0.022	0.046	0.979	0.888	1.065	.639
EFW centile	-0.012	0.01	0.988	0.969	1.007	.22
Parity	0.125	0.21	1.133	0.714	1.63	.552
Sex	0.158	0.386	1.172	0.553	2.55	.681
GA at examination	-0.093	0.076	0.911	0.781	1.056	.221
CPR MoM	-1.827	0.745	0.161	0.035	0.654	.014

Detection rate of 21.43% for a false-positive rate of 5%
 Detection rate of 32.14% for a false-positive rate of 10%
 AUC 0.663, 95% CI [0.545, 0.782]
 AIC = 306.556

OR: odds ratio; Std. Error: standard error; Lower 95%: lower limit of the 95% confidence interval; Upper 95%: upper limit of the 95% confidence interval; BMI: body mass index; GA: gestational age; EFW: estimated fetal weight; CPR: cerebroplacental ratio; MoM: multiples of the median; DR: detection rate; FPR: false-positive rate; AUC: area under the ROC curve; 95% CI: 95% confidence interval; AIC: Akaike Information Criterion.

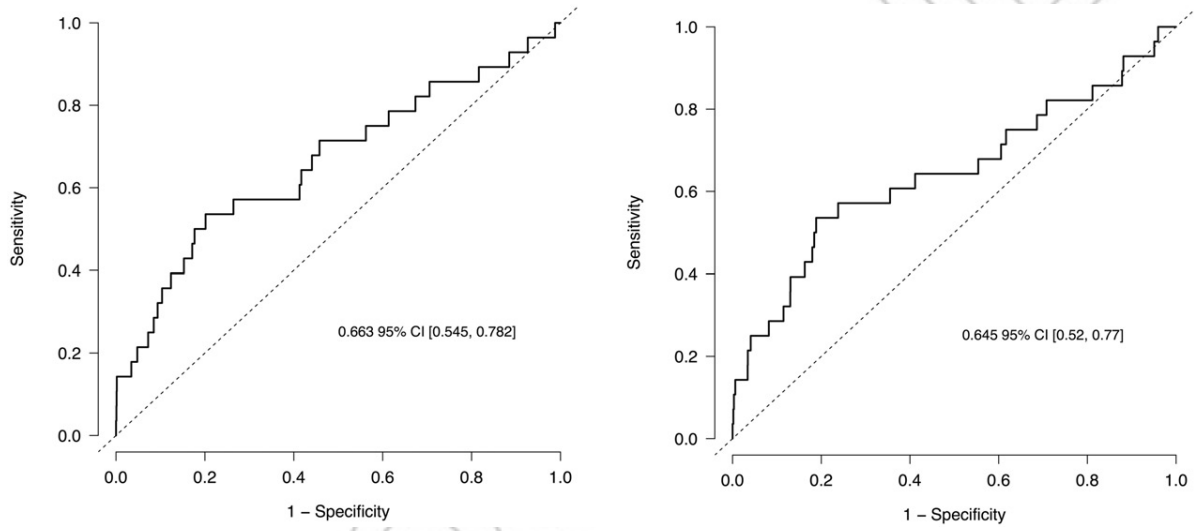


Figure 2. Receiver operating characteristic curves for the prediction of antepartum late stillbirth using multiples of the median for cerebroplacental ratio (left) and middle cerebral artery pulsatility index (right).

27.6% of stillborn fetuses presented a CPR below 0.6765 MoM (5th centile of CPR MoM [6]), 6.4% in the control group, ($p < .0001$), suggesting the existence of FRGP [6–8] in a considerable proportion of the cases (Figure 3). In order to better evaluate the importance of CPR MoM, we studied its components (UA PI and MCA PI MoM) separately in a second multivariate analysis (Table 3); in this model, only MCA MoM provided significant prediction of stillbirth and the AUC for prediction of stillbirth was 0.645 (Figure 2 right).

Discussion

Main findings of the study

This multicenter study of late antepartum stillbirths with antenatal assessment within 2 weeks of the adverse event has demonstrated that more than 70%

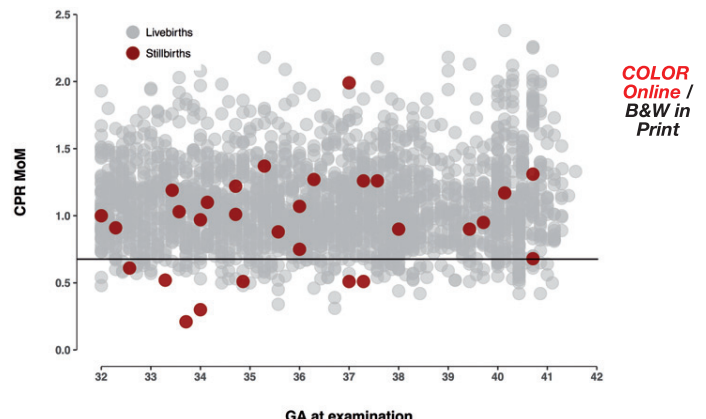


Figure 3. Scatter plot representing the CPR MoM according to gestational age. A notable proportion of stillborn fetuses (27.6%) present values below 0.6765 (<5th centile) suggesting the existence of a failure to reach the growth potential (6.4% in the control group, $p < .0001$).

Table 3. Model for stillbirth prediction using MCA PI and UA PI.

Variables	EFW according to local references					
	Estimate	Std. Error	OR	Lower 95%	Upper 95%	p-value
(Intercept)	1.09	3.212	2.975	0.006	1759.513	.734
Age	-0.033	0.035	0.968	0.904	1.038	.348
BMI	-0.023	0.046	0.977	0.887	1.064	.623
EFW centile	-0.012	0.01	0.988	0.969	1.008	.234
Parity	0.117	0.211	1.124	0.707	1.62	.578
Sex	0.123	0.387	1.131	0.532	2.465	.750
GA at examination	-0.066	0.078	0.937	0.801	1.09	.401
UA PI MoM	0.864	0.657	2.372	0.563	8.235	.189
MCA PI MoM	-2.26	1.038	0.104	0.013	0.735	.029
Detection rate of 25% for a false-positive rate of 5%						
Detection rate of 28.6% for a false-positive rate of 10%						
AUC 0.645, 95% CI [0.52, 0.77]						
AIC = 308.49						

OR: odds ratio; Std. Error: standard error; Lower 95%: lower limit of the 95% confidence interval; Upper 95%: upper limit of the 95% confidence interval; BMI: body mass index; GA: gestational age; EFW: estimated fetal weight; CPR: cerebroplacental ratio; MoM: multiples of the median; DR: detection rate; FPR: false-positive rate; AUC: area under the ROC curve; 95% CI: 95% confidence interval; AIC: Akaike Information Criterion.

are not SGA and that the only antenatal predictor of stillbirth is MCA PI. The performance of screening by MCA PI or CPR for the prediction of stillbirth is poor with DR of about 30% at FPR of 10%.

Interpretation of the findings and review of earlier studies

Previous studies reported that the risk of stillbirth increases with maternal age and BMI and it is also increased in primigravidas and multiparas [19–33]. Our results demonstrate that once CPR or MCA PI are taken into account, these maternal characteristics have no significant influence on stillbirth. Similarly, previous studies suggested that stillbirth is more common in male than female fetuses [34–37], but we found that fetal gender did not have a significant contribution to stillbirth. Finally, fetal smallness has also been related with stillbirth in earlier studies [19,33]. In this work, we did not find EFW to be relevant. In fact, according to recent publications, the true influence of smallness on stillbirth might be even lower than previously thought, as it could be due to dehydration processes leading to a quick loss of weight prior to delivery [38].

Our findings on the association between low MCA PI and CPR with stillbirth are in agreement with the results of previous studies [6–13,39,40], which relates adverse outcome with the existence of FRGP [6–8]. Conversely, other studies have not found CPR to be an important predictor of stillbirth [41,42]. The explanation for this controversy may be due to the type of study population; CPR may be very useful in pregnancies at high risk of FGR [39], but less in low-risk populations [5,41]. Further studies are required to clarify these associations.

Clinical and research implications

Assessment of fetal hemodynamics provides poor prediction of stillbirth. However, pregnancies with low-fetal MCA PI and CPR may require close followup because in some cases, there is increased risk of stillbirth. Further research is necessary to identify new potential markers that may improve prediction of late stillbirth.

Study strengths and limitations

The major strength of the study is the recording of data on fetal hemodynamics within a short time interval before fetal death. The limitations of the study are the low number of cases and the retrospective nature of the study, which avoided retrieval of some data in all cases, including maternal smoking, which is reported to be an important contributor to stillbirth [19].

In conclusion, MCA PI and CPR are the relevant parameters in the explanation of late antepartum fetal death. However, due to the weakness of the associations, the ability of the models to predict stillbirth remains poor.

Disclosure statement

No potential conflict of interest was reported by the authors.

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