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Is the Cerebro-Placental Ratio Sufficient to Predict Adverse Neonatal Outcome in Small for Gestational Age Fetuses > 34 Weeks of Gestation?

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Abstract: Fetuses with an estimated weight (EFW) below the 10th percentile are at risk for adverse perinatal outcome and clinical management remains a challenge. We examined EFW and cerebro-placental ratio (CPR) with regard to their predictive capability in the management and outcome of such cases. Fetuses were first diagnosed as small after 34 weeks of gestation with an actual EFW below the 10th percentile at our tertiary academic center. We determined the optimum cutoff value for CPR and EFW in predicting adverse neonatal outcome. Mean gestational age at diagnosis was 36 weeks. One hundred and two cases were included in our study. We determined a CPR of 1.4 and an EFW of 2152 g to be the best cutoff value for predicting adverse fetal outcome, with an area under the curve (AUC) of 0.65 (95% CI 0.54–0.76); $p = 0.009$, and 0.76 (95% CI 0.66–0.86); $p < 0.0001$, respectively. However, when comparing EFW with CPR, EFW seems to be slightly better in predicting adverse fetal outcome in our group. While the use of CPR alone for the management of small fetuses is not sufficient, it is an important additional tool that may be of value in the clinical setting.

Keywords: cerebro-placental ratio; Doppler; estimated fetal weight; fetal growth restriction; neonatal outcome; placental insufficiency

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1. Introduction

Fetal growth restriction (FGR) is associated with preterm delivery and an elevated risk for unfavorable perinatal and neonatal outcome [1,2]. There are several causes for FGR, including maternal, fetal and placental [3]. Neonatal morbidity includes asphyxia, hypoglycemia, hypothermia as well as increased perinatal mortality, along with a higher risk for operative delivery and neonatal intensive care unit (NICU) admission [2,4–6]. Furthermore, later neurological development may be impaired as well as physical growth in adulthood [1,2,7,8].

Consequently, optimal clinical management is crucial in timing of the delivery while minimizing adverse perinatal outcomes. In utero monitoring may include regular ultrasound exams with Doppler studies using the cerebro-placental ratio (CPR) [9–11]. CPR is an indicator of placental function (using the umbilical artery (UA)) and fetal adaptation to placental insufficiency (using the middle cerebral artery (MCA)) and is calculated as a ratio between the MCA pulsatility index (PI) and UA PI. A low CPR is a sign of cerebral redistribution and has been associated with adverse neonatal outcome [1]. Different cut-off values for CPR have been proposed in the daily clinical routine and it is unclear if an absolute cut-off value of CPR < 1 or gestational age-related CPR percentiles are a better predictor of the fetus' well-being [1,12].

Furthermore, several definitions for fetuses with FGR as well as small for gestational age (SGA) and intrauterine growth restriction (IUGR) are used, with 32 as well as 34 weeks of gestation set as a cutoff for late FGR [1,13–15]. Other definitions have been established by obstetric societies throughout the world, underlying the difficulties in finding a common and simple definition to distinguish the truly placental-related small fetus [3,16,17]. Recently, definitions for early and late FGR has been accepted based on an international Delphi consensus. This consensus defined late FGR starting at 32 weeks of gestation by an EFW or abdominal circumference (AC) below the 3rd percentile, or alternatively by an EFW or AC below the 10th centile or its flattening across more than 2 centiles, and/or abnormal CPR or uterine artery PI [13]. This definition has been subsequently also used by ISUOG, which added that Doppler examinations may be used to distinguish between FGR and SGA [14].

The objective of our retrospective study was to examine what CPR cutoff value is the best predictor for perinatal as well as neonatal outcome in small fetuses > 34 weeks of gestation. In addition, we looked at how it compares together with estimated fetal weight.

2. Materials and Methods

2.1. Study Design

This retrospective single center cohort study was conducted at the Department of Obstetrics and Gynecology, Bern University Hospital, Switzerland. Cases between 2009 and 2016 were identified using our obstetric and neonatal databases. We searched our database for fetuses with an EFW below the 10th percentile after 34 weeks of gestation. We recorded ultrasound parameters at first diagnosis of FGR as well as parameters at the last ultrasound before birth. EFW was calculated using Hadlock IV formula [18]. Prenatal ultrasound and Doppler studies were conducted with a GE Voluson E8 and E10 (GE Voluson, Zipf, Austria) equipped with a C2–9, C1–5 MHz, or RM6C transabdominal transducer. Ultrasound examinations were performed or supervised by an expert sonographer, defined as a consultant with at least three years ultrasound experience. Doppler flow velocity waveforms were recorded during fetal apnea, and when at least three consecutive waveforms showing a consistent pattern were obtained, UA and MCA PI were obtained. The high-pass filter was set at 60–90 Hz. The size of the sample volume was adapted to the vessel diameter. CPR was calculated using the MCA PI/UA PI.

We recorded maternal and peripartal parameters as well as neonatal outcome. Maternal parameters included medical and obstetric history including parity, current as well as prior pregnancy complications, such as gestational diabetes, stillbirth, prior delivery with a birth weight below the 10th centile, pre-eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome or other placental pathologies. Categorization of ethnicity was performed according to the Fetal Medicine Foundation [19,20]. Gestational hypertension and preeclampsia were defined according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) [21].

2.2. Inclusion Criteria

We included singleton pregnancies with an EFW below the 10th percentile first diagnosed between 34 0/7 and 38 0/7 weeks of gestation, with subsequent delivery at our hospital.

2.3. Exclusion Criteria

Fetuses with an EFW < 10th percentile and/or pathological ACM or UA Doppler ultrasound before 34 0/7 or after 38 0/7 week of gestation, congenital anomalies, chromosomal defects, intrauterine infections, antepartum stillbirth, and multiple pregnancies were excluded.

2.4. Neonatal Outcome

Neonatal outcome included birth weight (BW), head circumference and length, gender, Apgar score at 5 min, and umbilical artery pH. Neonatal acidosis at birth was defined as umbilical artery pH below 7.15 and severe acidosis as below 7.0. Data on neonatal morbidity included hyperbilirubinemia, neonatal anemia, hypoglycemia, hypothermia, apnea-bradycardia-syndrome, and respiratory distress syndrome. Duration of NICU hospitalization was recorded as well.

The value of the CPR and EFW in predicting outcome was calculated dichotomizing our collective into cases with good and those with adverse outcome. Adverse neonatal outcome was defined as Apgar < 7 at 5 min, and/or umbilical artery pH < 7.15 and/or NICU admission (requiring intravenous lines for treatment, additional respiratory support, additional intensive observation) and/or neonatal morbidity with at least one of the following criteria: hypoglycemia, hyperbilirubinemia, respiratory distress syndrome (RDS), apnea-bradycardia and hypothermia.

2.5. Standard Clinical Management

Management of suspected small fetuses in our clinic is mainly based on the severity of growth restriction, maternal comorbidities (e.g., hypertensive complications), Doppler findings and cardiotocography (CTG). We usually do not deliver below 37 weeks of gestation when the feto-placental hemodynamics are compensated, namely, an umbilical artery PI below the 95th percentile for gestational age and no sign of fetal distress is evident during CTG-monitoring. If the EFW is above the 5th percentile, then we usually schedule induction of labor or a Cesarean section around 38 to 39 weeks of gestation, if the EFW is below the 5th centile then it is a week earlier. During the time our cases were collected for this study, MCA Doppler was not incorporated within our management practices. Similarly, we did not use angiogenic information for clinical management purposes.

2.6. Stasticial Analysis

Statistical analysis was performed using GraphPad Prism version 8 for Windows (GraphPad Software, San Diego, CA, USA, www.graphpad.com). Correlations were searched by using Spearman rank correlation, while proportions were analyzed by Chi^2 test or Fischer's exact test where appropriate. The Mann–Whitney test was used to analyze continuous variables. Receiver operating characteristic (ROC) curve analysis was used to describe the relationship between the sensitivity and false-positive rate for estimated fetal weight as well for the CPR in predicting adverse neonatal outcome. Statistical significance was considered achieved when $p < 0.05$.

3. Results

A total of 128 cases were identified fulfilling the inclusion criteria, with 125 used for further analysis as three were incorrectly classified as small but actually had an EFW > 10th percentile. One hundred and five had a recorded CPR in the last ultrasound before delivery, while 102 had both a recorded CPR as well as EFW and were included in the final analysis.

3.1. Demographic Data

Demographic and peripartal data are summarized in Table 1. Gestational and pre-gestational diabetes, hypertension and current pre-eclampsia were found in about 10% each, respectively. More than half of the women delivered via Cesarean section (CS) (57.8%). However, in the group with good neonatal outcome, there were fewer CS than in the adverse neonatal group (49% versus 70%, respectively). As this was a retrospective study, there was no standardized clinical management.

Table 1. Demographic and peripartal data.

Variables	N (%)
Age (years)	34 ± 6.8
Ethnicity (white)	86 (84.3%)
Primiparity	60 (58.8%)
Assisted reproductive technology	3 (2.9%)
Body mass index (BMI) ≥ 30kg/m^2	5 (4.9%)
Smoking	23 (22.5%)
Pre-gestational and gestational diabetes	12 (11.8%)
Hypertension (chronic and gestational)	12 (11.7%)
Renal disease	2 (2%)
Autoimmune disease	3 (3%)
Prophylactic aspirin intake	8 (7.8%)
Previous PE/HELLP	6 (5.9%)
Prior delivery with BW below the 10th centile and IUFD	2 (1.9%)
Prior delivery with BW below the 10th centile	23 (22.5%)
PE/HELLP in current pregnancy	10 (9.8%)
GA at birth (weeks ± days)	37.6 ± 11.3
Delivery ≥ 37 weeks of gestation	71 (70%)
Mode of delivery	
Spontaneous vaginal delivery	34 (33.3%)
Instrumental vaginal delivery	9 (8.8%)
Cesarean section	59 (57.8%)
Predicted/confirmed BW below 10th percentile	90 (88%)
Birth weight (g)	2281 ± 388

Data are presented as n (%) or mean ± standard deviation, unless stated otherwise. BW, birth weight; PE, preeclampsia; HELLP, hemolysis, elevated liver enzymes, low platelets; SGA, small for gestational age; IUGR, intrauterine growth retardation; IUFD, intrauterine fetal death; GA, gestational age.

3.2. Ultrasound Parameters

Mean gestational age at diagnosis was 36 weeks of gestation. The mean CPR was 1.5 at the last ultrasound examination before birth. The mean time interval between last ultrasound and delivery was 3.3 days. Overall, 88% of our cases had an EFW below the 3rd percentile (therefore also fulfilling the actual definition of late FGR [14]), while 9 cases (8.8%) had an EFW > 3rd and < 10th centile for gestational age. Five of those nine cases had a diagnosis of late flattening. Further ultrasound parameters before delivery are summarized in Table 2.

Table 2. Parameters at last ultrasound before delivery.

Variables	N (%)
GA at diagnosis (weeks ± days)	36.0 ± 1.1
GA at last ultrasound before delivery (weeks ± days)	37.0 ± 1.4
EFW (g)	2209 ± 366
EFW < 3rd percentile	90 (88%)
EFW < 10th and ≥ 3rd percentile	9 (8.8%)
EFW > 10th percentile	3 (2.9%)
CPR at last ultrasound before delivery	1.53 ± 0.5
Middle cerebral artery PI	1.44 ± 0.3
Umbilical artery PI	1.0 ± 0.3
Time interval between last ultrasound and delivery (days)	3.31 ± 3.4

Data are presented as n (%) or mean ± standard deviation, unless stated otherwise. GA, gestational age; EFW, estimated fetal weight; CPR, cerebro-placental ratio; PI, pulsatility index.

3.3. Neonatal Outcome

Neonatal outcomes are summarized in Table 3. Adverse fetal outcome was defined as described above. Forty-three cases had an adverse neonatal outcome. Of those, 56% were preterm deliveries below 37 weeks of gestation. Approximately 88% of cases in each of the two groups were predicted and postnatally confirmed as small for gestational age. The most frequent morbidities were hypoglycemia, hyperbilirubinemia and respiratory distress syndrome. Overall, 79% of cases in the adverse outcome group were hospitalized in the NICU for a median of 10 days (range 0 to 88 days).

Table 3. Adverse and good neonatal outcome.

Variables	Adverse Outcome N = 43	Good Outcome N = 59	*p* Value
GA at last ultrasound (weeks ± days)	36.1 ± 8.8	37.4 ± 8.5	<0.001
Time interval last ultrasound to delivery (days)	2.4 ± 2.8	4.0 ± 3.6	0.017
CPR at last ultrasound	1.4 (0.49)	1.6 (0.48)	0.014
GA at delivery (weeks ± days)	36.6 ± 10.0	38.4 ± 9.6	<0.001
Preterm delivery (<37 weeks)	24 (56%)	7 (12%)	<0.001
Female gender	21 (49%)	36 (61%)	0.23
Birth weight (g)	2059 ± 361	2443 ± 325	<0.001
Birth weight percentile groups (FGR)			
<3rd centile	22 (51%)	26 (44%)	
<10th and ≥3rd percentile	17 (40%)	28 (47%)	
≥10th percentile	4 (9.3%)	5 (8.5%)	
Predicted/confirmed birth weight < 10th percentile	38 (88%)	52 (88%)	1.00
Mode of delivery			
Spontaneous vaginal delivery	9 (21%)	25 (42%)	0.033
Instrumental vaginal delivery	4 (9.3%)	5 (8.5%)	1.00
Cesarean section	30 (70%)	29 (49%)	0.044
Arterial cord pH			
pH < 7.15	6 (14%)	0 (0.00%)	0.005
Apgar at 5 min < 7	3 (7.0%)	0 (0.00%)	0.07
NICU admission	34 (79%)	0 (0.00%)	<0.001
Duration of NICU hospitalization	10 (0–88) *	0	
Neonatal morbidity (overall)	32 (74%)	0 (0.00%)	<0.001
Hypoglycemia	15 (35%)	0 (0.00%)	<0.001
Hyperbilirubinemia	13 (30%)	0 (0.00%)	<0.001
Respiratory distress syndrome	8 (19%)	0 (0.00%)	<0.001
Apnea-bradycardia	7 (16%)	0 (0.00%)	0.002
Hypothermia	2 (4.7%)	0 (0.00%)	0.18

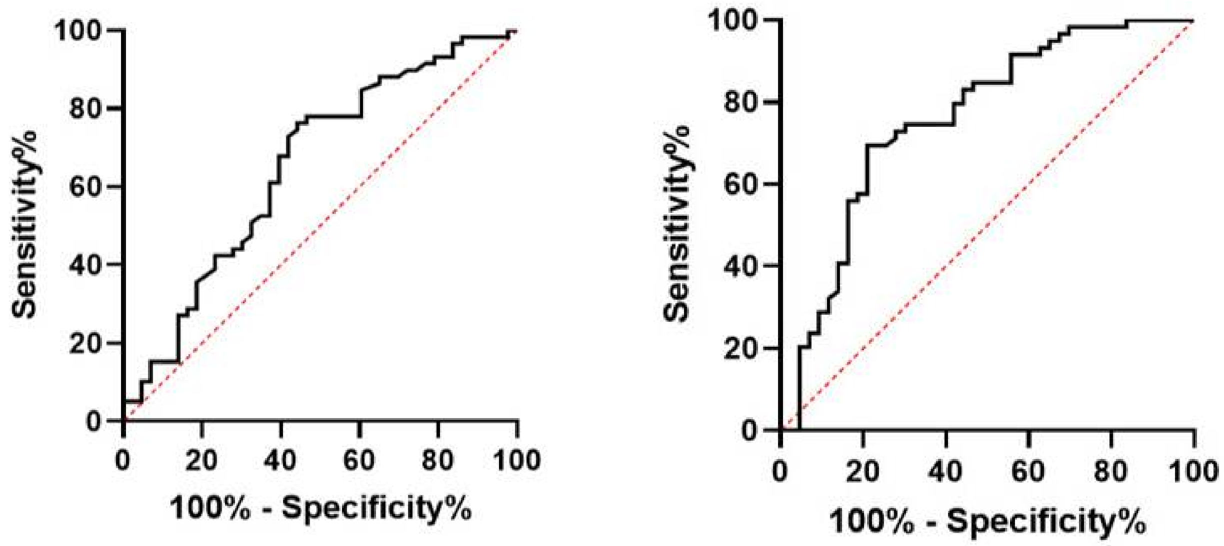
Data are presented as n (%) or mean ± standard deviation, unless stated otherwise; * range. GA, gestational age; CPR, cerebro-placental ratio; FGR, fetal growth restriction; NICU, neonatal intensive care unit.

3.4. CPR Cutoff Value and EFW

As expected, CPR and EFW differed significantly between the two groups (good and adverse outcome) and were correlated significantly (r = 0.23, $p = 0.02$). Therefore, we were able to calculate ROC curves for CPR and EFW, with an AUC of 0.65 (95% CI 0.54–0.76) for CPR and 0.76 (95% CI 0.66–0.86) for EFW, respectively, as shown in Figure 1a,b.

As shown in Figures 2 and 3, CPR < 1.4 seems to be the best discriminator between good and adverse outcome in our cohort. Similarly, a low EFW (<2152 g) is significantly related to adverse fetal outcome. Both CPR and EFW are good predictors for adverse fetal outcome, however, EFW < 2152 g (OR 7.8, 95% CI 3.3–19.74; $p < 0.0001$) shows higher odds compared to CPR < 1.4 (OR 2.9, 95% CI 1.23–6.72; $p < 0.01$).

To correct for gestational age and as suggested in a previous study on CPR, we transformed CPR absolute values into multiple of median (MoM) values. However, we did not see any differences in our results after transformation into CPR MoM values [22]. For those nine cases with an EFW between >3rd and <10th centile, CPR was at 1.78 ± 0.1 MoM. Furthermore, the MCA PI was 1.46 ± 0.27. These cases did not fulfill the newer concept of defining late FGR. However, five of them showed a growth projection with crossing centiles.



(**a**) (**b**)

Figure 1. Receiver-operating characteristics (ROC) curves for performance in predicting adverse neonatal outcome using (**a**) CPR (AUC 0.65, 95% CI 0.54–0.76, $p = 0.009$); and (**b**) EFW (AUC 0.76, 95% CI 0.66–0.86, $p < 0.000$).

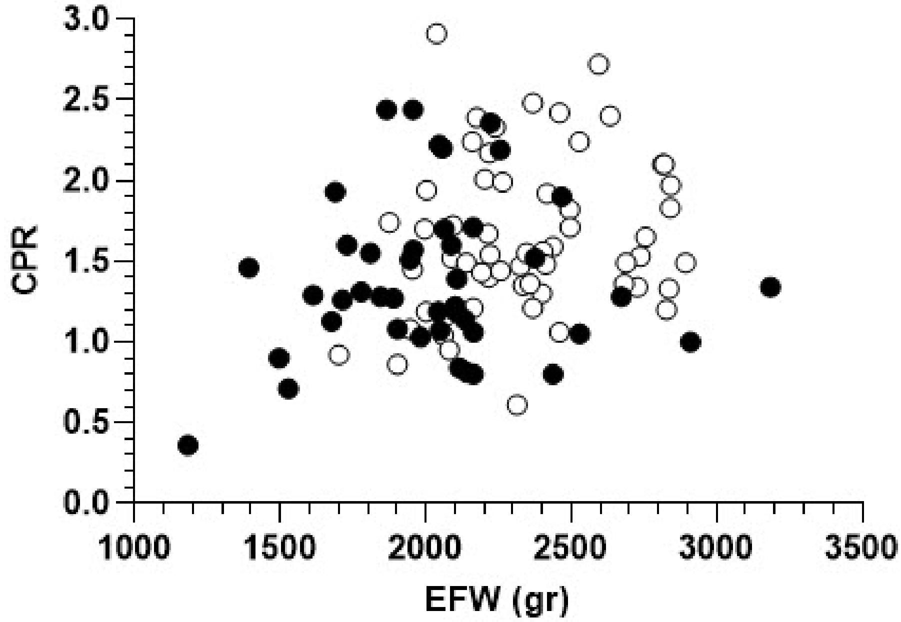


Figure 2. Correlation between cerebro-placental ratio (CPR) and estimated fetal weight (EFW) for neonates with good and adverse outcomes. Black dots represent cases with adverse fetal outcome, white dots show cases with good fetal outcome.

3.5. Umbilical Artery PI

UA PI > 95th percentile was present in 7/43 (16%) cases with adverse outcome and in 4/59 (7%) cases with good fetal outcome. In those cases with adverse outcome, all seven had a CPR < 1.4 and five cases also had an EFW < 2152 g. All four cases with a good outcome had a CPR < 1.4 and only three cases had an EFW < 2152 g as well. None of our cases had absent or reverse end-diastolic flow in the umbilical artery.

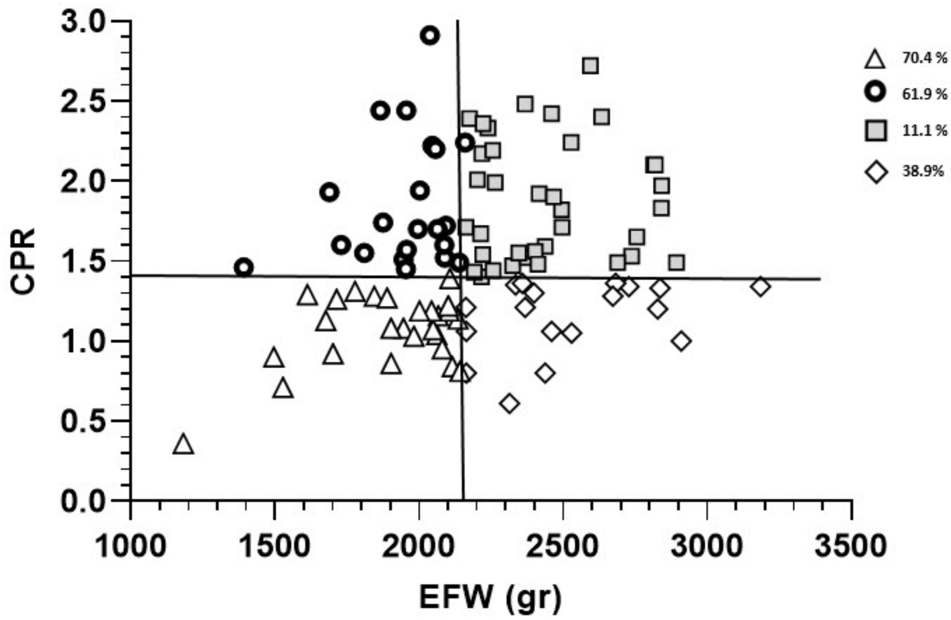


Figure 3. Classification of groups according to cerebro-placental ratio (CPR) and estimated fetal weight (EFW), irrespective of outcome. Numbers shown in % on the right are adverse fetal outcomes for each group. For example, in the group with a CPR < 1.4 and EFW < 2152 g, 19/27 (70.4%) cases had an adverse fetal outcome.

4. Discussion

Our study confirms that the EFW and the CPR are able to distinguish between good and adverse neonatal outcome in pregnancies complicated by placental insufficiency $\geq$ 34 weeks of gestation. Indeed, a CPR of <1.4 and an EFW of <2152 g significantly differentiate between both groups. The combination of these parameters, which are both easily measurable during fetal surveillance, shows a better performance than using just one single parameter. The highest incidence of neonates fulfilling our criteria for adverse outcome were found in the group with CPR < 1.4 and EFW < 2152 g. In this group, almost three-quarter of cases had an adverse outcome while only 11.1% were found in the group with a CPR > 1.4 and EFW > 2152 g.

Several randomized studies have examined early fetal growth restriction below 34 weeks of gestation. Most prominently, the TRUFFLE study for outcome in early FGR fetuses recommends monitoring using CTG and arterial and venous fetal Doppler studies [5]. Based on the results from the TRUFFLE as well as GRIT trials, clinical diagnosis and a management algorithm for early and severe FGR has been proposed. However, neither the TRUFFLE nor the GRIT trial used MCA and CPR as a parameter for management of early FGR, but instead focused on Doppler flow in the ductus venosus and UA, as well the short-term variability calculated by computerized CTG evaluation in addition to gestational age [5,23]. The various instruments that are used to monitor fetal wellbeing reflect the different phenotypes of early and late FGR fetuses and their different adaptive strategies on the underlying placental dysfunction.

A recent meta-analysis suggests a benefit in using CPR to predict adverse outcome in FGR, however, without suggesting a CPR cutoff value [7]. Factors that might affect these Doppler measurements were examined as well: low CPR is associated with low maternal BMI, ethnicity (white), in-vitro fertilization, smoking, chronic hypertension, pregestational diabetes type I, and nulliparity, while CPR is higher in multiparous women [24]. However, there is insufficient data regarding management for late FGR. The DIGITAT trial was planned to investigate the neonatal outcome of FGR after 36 weeks of gestation, and suggests that expectant management with increased fetal monitoring is not superior to induction of labor [25]. Our detection rate of small for gestational age neonates was better compared to that of the DIGITAT trial, however, our selected study cohort was assessed retrospectively based on our inclusion criteria. Another recent prospective observational study examined cerebral Doppler changes in FGR and was able to show that cerebral Doppler changes before delivery are associated with adverse short-term neonatal outcome in FGR as well [26].

The classic flattening of the fetal growth dynamics was one of the most important features of our cases. Moreover, in most cases placental pathologic results were available and in 37.3% of our cases the placental weight was also below the 10th percentile. Therefore, our study population is not comparable to a population selected by a screening setting were the fetus is seen only once. Indeed, the incidence of small neonates in the DIGITAT study was 65%. This methodologic difference may explain why our calculated CPR cutoff is higher than other published values. Moreover, none of our cases had a UA PI above the 95th percentile. This is also a major difference compared to many studies dealing with late FGR and CPR [1,12,27]. However, our results are in line with a recently published study, confirming that gestational age as well as birth weight are good predictors of adverse neonatal outcome and that cerebral blood flow seems to play an important role [26]. In addition, recent guidelines established CPR as a complementary parameter for managing late FGR [13]. In contrast, uterine artery Doppler does not seem to play an important enough role in managing late FGR, as both of these aforementioned studies have shown. Therefore, we have not included uterine artery Doppler in our analysis, even though it is part of our routine ultrasound examination for FGR.

One weakness of our study is its retrospective character and a relatively small sample size. This is also due to our selective cohort where we specifically looked at fetuses with pre-selected EFW. Placental insufficiency as a main cause for FGR was predominant in our cohort. However, compared with the TRUFFLE study, maternal hypertensive complications were relatively low in our cohort [5]. Furthermore, when we started our study, the definition of "late FGR" was not yet set as it is today. We determined our inclusion criteria and FGR definition based on the expert review of DeVore [1]. Therefore, we defined and included "late FGR" cases with an EFW below the 10th percentile and a gestational age $\geq$ 34 weeks and 0 days as opposed to the Delphi consensus using 32 weeks and 0 days of gestation and an EFW (or abdominal circumference) < 3rd centile [13]. However, most of our cases do already fulfill even the newer proposed criteria for "late FGR" as a high percentage of our fetuses had an EFW < 3rd centile and notably, were also small at delivery. Our results are also in accordance with a recently published bigger study using similar inclusion criteria [26]. Of note, the positive predictive value of a SGA neonate using the 10th centile in our center was 90/102 (88%) which is significantly higher than in the previously mentioned, much bigger study [28]. Molina et al. compared both strategies by prenatally defining a small fetus using the Delphi consensus versus an EFW < 10th centile. Their conclusion was that the new consensus definition detects fewer cases of neonatal SGA than does the definition based on an EFW < 10th centile, but is associated with a slight improvement in predicting adverse neonatal outcome [28].

In conclusion, it is important to detect small fetuses in the third trimester and define parameters for delivery indication to minimize adverse perinatal outcomes. A combination of EFW and CPR, using our cutoff value of 2152 g and 1.4, respectively, might help in determining the optimum time for delivery in order to minimize neonatal morbidity for fetuses with an EFW < 10th percentile $\geq$ 34 weeks of gestation. Estimated fetal weight as well as gestational age seem to be the most important criteria for clinical management of FGR. Further prospective studies are needed to confirm our results, which would also take neurodevelopmental outcomes of children exposed to placental insufficiency during fetal life into account, another important factor regarding long-term morbidity [12,29,30].

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Informed Consent Statement: Patient consent was waived as it is a retrospective study without risks to the participants, evaluating and improving current clinical management.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy reasons.

Conflicts of Interest: The authors declare no conflict of interest.

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