Prognostic Value of Cerebroplacental Ratio in Appropriate-for-Gestational-Age Fetuses Before Induction of Labor in Late-Term Pregnancies

Vorhersagekraft der cerebro-plazentaren Ratio bei normalgewichtigen Föten vor Einleitung bei Terminüberschreitung

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ABSTRACT

Purpose To evaluate the relationship between cerebroplacental ratio (CPR) and the need for operative delivery due to intrapartum fetal compromise (IFC) and adverse perinatal outcome (APO) in appropriate-for-gestational-age (AGA) late-term pregnancies undergoing induction of labor. The predictive performance of CPR was also assessed.

Materials and Methods Retrospective study including singleton AGA pregnancies that underwent elective induction of labor between 41 + 0 and 41 + 6 weeks and were delivered before 42 + 0 weeks. IFC was defined as persistent pathological CTG or pathological CTG and fetal scalp pH < 7.20. Operative delivery included instrumental vaginal delivery (IVD) and cesarean section (CS). APO was defined as a composite of umbilical artery pH < 7.20, Apgar score < 7 at 5 minutes, and admission to the neonatal intensive care unit for > 24 hours.

Results The study included 314 women with 32 (10 %) IVDs and 49 (16 %) CSs due to IFC and 85 (27 %) APO cases. Fetuses with CPR < 10th percentile showed a significantly higher rate of operative delivery for IFC (40 % (21/52) vs. 23 % (60/262); p = 0.008) yet not a significantly higher rate of APO (31 % (16/52) vs. 26 % (69/262); p = 0.511). The predictive values of CPR for operative delivery due to IFC and APO showed sensitivities of 26 % and 19 %, specificities of 87 % and 84 %, positive LRs of 2.0 and 1.2, and negative LRs of 0.85 and 0.96, respectively.

Conclusion Low CPR in AGA late-term pregnancies undergoing elective induction of labor was associated with a higher risk of operative delivery for IFC without increasing the APO rate. However, the predictive value of CPR was poor.

ZUSAMMENFASSUNG

Ziel Auswertung der Assoziation zwischen cerebro-plazentarer Ratio (CPR) und Notwendigkeit einer operativen Entbindung wegen intrapartalem fetalem Distress (IFD) sowie schlechtem perinatalem Outcome bei normalgewichtigen Föten vor Einleitung bei Terminüberschreitung. Die prädiktive Aussagekraft der CPR wurde analysiert.

Material und Methode Retrospektive Studie von Einlingsgraviditäten, die zwischen 41 + 0 und 41 + 6 Schwangerschaftswochen eingeleitet wurden und vor 42 + 0 Schwangerschaftswochen entbunden wurden. IFD wurde als persistierend pathologisches CTG oder pathologisches CTG und Mikroblutuntersuchung < 7,20 definiert. Die operative Entbindung umfasste sowohl vaginal-operative Entbindungen als auch Sectio caesareas. Schlechtes perinatales Outcome wurde als das Vorhandensein eines Nabelschurarterie-pH-Wertes < 7,20, Apgar-Wertes < 7 nach 5 Minuten und/oder eine Aufnahme auf die Neugeborenenstation > 24 Stunden definiert.

Ergebnisse Insgesamt wurden 314 Gebärende eingeschlossen. Von denen hatten 32 (10 %) eine vaginal-operative Entbindung und 49 (16 %) Sectiones, jeweils wegen IFD, sowie 85 (27 %) ein schlechtes perinatales Outcome. Föten mit CPR

< 10 Perzentile zeigten einen signifikant höheren Anteil an operativen Entbindungen (40 % (21/52) vs. 23 % (60/262); p = 0,008) sowie einen nicht signifikant höheren Anteil an schlechtem perinatalem Outcome (31 % (16/52) vs. 26 % (69/262); p = 0,511). Die Vorhersagekraft der CPR für operative Entbindung wegen IFD und schlechtes perinatales Outcome zeigte jeweils eine Sensitivität von 26 % und 19 %, eine Spezifität von 87 % und 84 %, ein positives Wahrscheinlichkeitsverhältnis von 2,0 und 1,2 und ein negatives Wahrscheinlichkeitsverhältnis von 0,85 und 0,96.

Schlussfolgerungen Eine niedrige CPR bei normalgewichtigen Föten vor elektiver Einleitung bei Terminüberschreitung war mit einem höheren Risiko für eine operative Entbindung wegen IFD assoziiert. Das Risiko eines schlechten perinatalen Outcomes war nicht signifikant erhöht. Die Vorhersagekraft der CPR war jedoch niedrig.

Introduction

Late-term pregnancy is defined as a gestation occurring between 41 + 0 and 41 + 6 weeks [1]. It is associated with increased perinatal morbidity and mortality [2]. Thus, close fetal monitoring and induction of labor are usually performed. However, there is no evidence that antenatal cardiotocography and evaluation of amniotic fluid volume reduce the rate of adverse perinatal outcome (APO) [3, 4]. The risks of stillbirth and neonatal mortality at term increase with advancing gestational age [5, 6]. Recently published multicenter randomized trials including 4561 women showed that induction of labor at 41 weeks of gestation reduced perinatal morbidity and mortality compared with expectant management and induction of labor at 42 weeks [7, 8]. Nevertheless, antenatal identification of fetuses at higher risk for intrapartum hypoxia remains challenging.

Lately, cerebroplacental ratio (CPR) has been proposed as a fetal surveillance tool in term pregnancies [9]. A low CPR reflects redistribution of fetal cardiac output towards the brain secondary to placental underperfusion. It has been associated with APO both in small-for-gestational-age (SGA) and in appropriate-for-gestational-age (AGA) fetuses [10, 11]. This suggests the presence of placental insufficiency in both groups. Although most published series have focused on SGA fetuses, the detection of unapparent placental dysfunction due to supposed normal growth in AGA fetuses is of great clinical relevance.

The aim of this study was to evaluate the association between CPR and operative delivery for intrapartum fetal compromise (IFC) and APO in AGA late-term pregnancies which underwent elective induction of labor. Moreover, the predictive performance of CPR for operative delivery due to IFC and APO was assessed.

Methods

We performed a retrospective study between March 2012 and December 2017. Singleton pregnancies with AGA fetuses in cephalic presentation with CPR measurement within one week of delivery that underwent elective induction of labor between 41 + 0 and 41 + 6 weeks due to late-term pregnancy with delivery before 42 + 0 weeks were included. Gestational age (GA) was calculated by first-trimester crown-rump length. In all women, CPR was measured before induction of labor, which was carried out with a dinoprostone vaginal insert or misoprostol vaginal insert, followed by amniotomy and/or oxytocin infusion if needed. AGA was defined as a birth weight (BW) between the 10th and 90th percentile [12]. Fetuses with chromosomal or anatomical abnormalities, oligohydramnios (amniotic fluid index ≤ 5 cm), women with elective cesarean section (CS), CS for failed induction, and patients with abnormal labor progression, preexisting conditions (hypertension, diabetes mellitus, connective tissue diseases, thrombophilia), or obstetric complications (gestational hypertension, preeclampsia, gestational diabetes mellitus) were excluded. The study protocol was approved by the hospital ethics committee (protocol number: 612/19 S).

Fetal Doppler assessment was routinely performed according to our institutional ultrasound protocol for pregnant women at ≥ 40 + 0 weeks of gestation using a Voluson E8 (GE Medical Systems, Solingen, NRW, Germany) or a Voluson E10 (GE Medical Systems, Solingen, NRW, Germany) with 6–4-MHz curvilinear abdominal transducer including the umbilical artery (UA) pulsatility index (PI) and the middle cerebral artery (MCA) PI in all cases. Doppler measurements were obtained from a free-floating portion of the umbilical cord and the proximal third of the MCA with the angle of insonation as close to zero as possible, a wall motion filter of 70 Hz, mechanical and thermal indices below 1, and during absence of fetal movements. Doppler PI was performed from at least three consecutive waveforms. CPR was calculated as MCA PI/UA PI. A CPR < 10th percentile was considered abnormal based on a better performance for the detection of CS for IFC and APO in low-risk pregnancies at term when compared to CPR < 5th percentile or CPR < 1 [13].

IFC was defined as persistent pathological CTG or the combination of pathological CTG and fetal scalp pH < 7.20. Operative delivery included IVD and CS. APO was defined as a composite of UA pH < 7.20, Apgar score < 7 at five minutes, and admission to the neonatal intensive care unit (NICU) for > 24 hours.

Recorded variables included maternal age, body mass index (BMI), parity, ethnicity, nicotine use, GA at ultrasound examination, UA PI, MCA PI, CPR, CPR percentile [14, 15], use of oxytocin for labor augmentation, CTG assessment [16], fetal scalp pH, mode of delivery, GA at delivery, sex, BW, BW percentile [12], UA pH, Apgar score at five minutes, and admission to NICU.

The normality of the data was assessed with the Shapiro-Wilk test. Since all continuous variables were not normally distributed, the Mann-Whitney U test was performed. Pearson's chi-square or Fisher's exact test were used to compare categorical data. All tests were two-tailed. P-values < 0.05 were considered statistically significant. Data analysis was performed using the Statistical Package for the Social Sciences software (SPSS 24.0, SPSS Inc., Chicago, IL, USA). Population characteristics according to the mode of

▶ **Table 1** Characteristics of the study population according to the mode of delivery.

	operative delivery due to IFC		p
	no (n = 233)	yes (n = 81)	
maternal age (years)	32.4 (7)	33.1 (6.5)	0.635
BMI (kg/m^2)	22.4 (5.1)	22.9 (4.1)	0.432
nulliparity	137 (59)	66 (81)	< 0.001
caucasian	220 (94)	75 (93)	0.590
smoking	37 (16)	10 (12)	0.442
CPR	1.65 (0.63)	1.63 (0.66)	0.066
CPR percentile	42 (54)	38 (55)	0.071
CPR < 10th percentile	31 (13)	21 (26)	0.008
dinoprostone vaginal insert	197 (85)	69 (85)	0.891
oxytocin for augmentation of labor	104 (45)	42 (52)	0.262
GA at delivery (weeks)	41.3 (0.3)	41.4 (0.3)	0.406
CPR to delivery interval (days)	3 (3)	3 (4)	0.906
induction of labor to delivery interval (days)	1 (1)	1 (0)	0.229
male	104 (45)	45 (56)	0.090
birth weight (g)	3590 (478)	3440 (345)	< 0.001
birth weight percentile	42 (37)	28 (24)	< 0.001

Data are given as median (interquartile range) or n (%). IFC: intrapartum fetal compromise; BMI: body mass index; CPR: cerebroplacental ratio; GA: gestational age.

delivery and perinatal outcome were compared. Moreover, multivariate logistic regression analysis was performed to identify predictors of operative delivery for IFC and APO using maternal age, BMI, parity, ethnicity, nicotine use, CPR percentile, use of oxytocin for labor augmentation, GA at delivery, sex, and BW percentile as independent variables. Furthermore, the study population was grouped according to CPR percentile (< 10th percentile and ≥ 10th percentile). Rates of operative delivery for IFC and APO were compared between the groups. Finally, predictive value of CPR for operative delivery due to IFC and APO was evaluated using the 10th percentile for definition of risk groups. Sensitivity, specificity, and likelihood ratios (LRs) were calculated.

Results

During the study period, a total of 314 women met the inclusion criteria. Overall, 52 (17 %) fetuses showed CPR < 10th percentile. Induction of labor was performed with a dinoprostone vaginal insert in 266 (85 %) women and with a misoprostol vaginal insert in 48 (15 %) women. The median interval between CPR assessment

▶ **Table 2** Multivariate logistic regression analysis of predictors of operative delivery for intrapartum fetal compromise.

	OR	95 % CI	p
maternal age (years)	1.031	0.974–1.091	0.296
BMI (kg/m^2)	1.021	0.957–1.090	0.527
nulliparity	3.612	1.739–7.501	0.001
caucasian	1.858	0.599–5.767	0.284
smoking	1.250	0.376–4.159	0.716
CPR percentile	1.000	0.990–1.009	0.929
oxytocin for augmentation of labor	0.514	0.280–0.941	0.031
GA at delivery (weeks)	1.771	0.441–7.123	0.421
male	1.562	0.874–2.793	0.132
birth weight percentile	0.975	0.960–0.990	0.002

OR: odds ratio; CI: confidence interval; BMI: body mass index; CPR: cerebroplacental ratio; GA: gestational age.

and delivery was 3 (interquartile range 3) days. Regarding operative delivery, 32 (10 %) women had IVD and 49 (16 %) underwent CS due to IFC. Indication for operative delivery was persistent pathological CTG in 72 (89 %) women and pathological CTG with fetal scalp pH < 7.20 in 9 (11 %) women. APO was observed in 85 (27 %) newborns including 75 cases with UA pH < 7.20, 6 cases with Apgar < 7 at five minutes, and 11 cases of NICU admissions (5 cases with neonatal infection, 5 cases with respiratory distress, 1 case with hypoglycemia).

Women with operative delivery due to IFC had a significantly higher proportion of nulliparity and CPR < 10th percentile as well as a significantly lower BW and BW percentile (▶ **Table 1**). Multivariate logistic regression identified nulliparity, use of oxytocin for augmentation of labor, and BW percentile as independent predictors of operative delivery due to IFC (▶ **Table 2**).

Pregnancies with APO showed a significantly higher rate of nulliparity and significantly lower rate of oxytocin for augmentation of labor (▶ **Table 3**). However, multivariate logistic regression did not identify independent predictors of APO (▶ **Table 4**).

Fetuses with CPR < 10th percentile showed a significantly higher rate of operative delivery due to IFC (40 % (21/52) vs. 23 % (60/262); p = 0.008). This statistically significant difference remained regardless of the type of operative delivery (IVD 23 % (9/40) vs. 10 % (23/225); p = 0.036, CS 28 % (12/43) vs. 15 % (37/239); p = 0.048). In addition, fetuses with CPR < 10th percentile did not have a significantly higher rate of APO (31 % (16/52) vs. 26 %

▶ **Table 3** Characteristics of the study population according to adverse perinatal outcome.

	adverse perinatal outcome		p
	no (n = 229)	yes (n = 85)	
maternal age (years)	32.6 (7.5)	33.0 (6.2)	0.891
BMI (kg/m^2)	22.8 (5.0)	22.1 (3.9)	0.156
nulliparity	139 (61)	64 (75)	0.016
caucasian	214 (93)	81 (95)	0.542
smoking	38 (17)	9 (11)	0.185
CPR	1.64 (0.63)	1.66 (0.58)	0.486
CPR percentile	42 (56)	42 (52)	0.463
CPR < 10th percentile	36 (16)	16 (19)	0.511
dinoprostone vaginal insert	196 (86)	70 (82)	0.479
oxytocin for augmentation of labor	116 (51)	30 (35)	0.015
GA at delivery (weeks)	41.3 (0.3)	41.3 (0.3)	0.698
CPR to delivery interval (days)	3 (3)	3 (3)	0.343
induction of labor to delivery interval (days)	1 (1)	1 (0)	0.181
male	107 (47)	42 (49)	0.672
birth weight (g)	3548 (408)	3510 (533)	0.600
birth weight percentile	38 (32)	36 (37)	0.428

Data are given as median (interquartile range) or n (%). IFC, intrapartum fetal compromise; BMI, body mass index; CPR, cerebroplacental ratio; GA, gestational age.

(69/262); p = 0.511). Analysis of the predictive value of CPR < 10th percentile for operative delivery for IFC and APO showed sensitivities of 26 % and 19 %, specificities of 87 % and 84 %, positive LRs of 2.0 and 1.2, and negative LRs of 0.85 and 0.96, respectively.

Discussion

This study showed that AGA fetuses with a low CPR before induction of labor due to late-term pregnancy had a significantly higher rate of operative delivery due to IFC without significant differences regarding APO. In addition, the value of CPR to predict main outcomes was low. To our knowledge, this is the first study evaluating CPR predictive value in low-risk pregnant women undergoing elective induction of labor between 41 + 0 and 41 + 6 weeks.

Physiological reduction of uteroplacental perfusion during uterine contractions is usually well tolerated in most fetuses due to activation of the peripheral chemoreceptors secondary to fetal hypoxia [17]. It leads to a reduction of oxygen consumption and centralization of cardiac output. However, fetuses with pre-labor impaired placental function are at higher risk for IFC due to lower glycogen stores, which limits the transition to anaerobic metabolism. Our data are in line with previous studies describing higher risk of operative delivery for presumed fetal distress in AGA fetuses at term (≥ 37 weeks of gestation) with a low CPR [18, 19]. These findings suggest mild placental insufficiency resulting in brain sparing. Recently published studies reported placental histopathological lesions from fetuses at term with growth restriction [20]. Thus, normal size does not necessarily mean normal growth. Since we evaluated late-term pregnancies, placental aging can be another relevant factor leading to IFC. Physiologic trophoblast apoptosis increases throughout pregnancy [21]. Furthermore, placental underperfusion accelerates apoptosis in the trophoblasts resulting in greater placental dysfunction [22, 23].

We showed that the proportion of CPR < 10th percentile was similar in pregnancies with and without APO. However, we acknowledge that the prevalence of APO in our population was low. Our data are in accordance with those of D'Antonio et al., who evaluated CPR at 41 + 3 weeks of gestation in "low-risk" pregnancies excluding fetuses with estimated fetal weight < 5th percentile, anhydramnios, and maternal comorbidities [24]. Women underwent induction of labor at 42 completed weeks of gestation and delivered at a median GA of 42 + 0 weeks. They reported no differences in the frequency of CPR < 5th percentile between preg-

▶ **Table 4** Multivariate logistic regression analysis of predictors of adverse perinatal outcome.

	OR	95 % CI	P
maternal age (years)	1.023	0.970–1.080	0.404
BMI (kg/m^2)	0.941	0.877–1.010	0.093
nulliparity	1.621	0.849–3.095	0.143
caucasian	0.619	0.168–2.284	0.472
smoking	1.584	0.497–5.055	0.437
CPR percentile	1.000	0.991–1.009	0.957
oxytocin for augmentation of labor	1.712	0.961–3.050	0.070
GA at delivery (weeks)	0.668	0.183–2.446	0.543
male	0.925	0.538–1.592	0.779
birth weight percentile	1.004	0.991–1.017	0.558

OR: odds ratio; CI, confidence interval; BMI, body mass index; CPR, cerebroplacental ratio; GA, gestational age.

nancies with normal and adverse fetal outcome defined as UA pH < 7.15 with a base deficit of 11 mM/L or CS for intrapartum ST analysis abnormalities. Conversely, Fiolna et al. found a higher proportion of CPR < 10th percentile in cases with adverse neonatal outcome in comparison to those without in AGA pregnancies undergoing induction of labor [25]. This could be due to the inclusion of women with preexisting conditions and obstetrics complications as well as a broader GA range at induction of labor (≥ 37 weeks) in the latter study.

Our study revealed a low predictive value of CPR regarding operative delivery due to IFC and APO. These findings are in agreement with a prospective study including 4944 singleton pregnancies with CPR assessment between 35 and 37 weeks of gestation and delivery between 39 and 41 weeks of gestation reporting poor performance of CPR in the prediction of fetal distress during labor leading to cesarean section both in infants with BW < 10th percentile and BW ≥ 10th percentile [26]. Furthermore, a recent meta-analysis including 22 studies with 4301 single pregnancies and suspected fetal growth restriction showed that CPR prognostic accuracy was low for adverse perinatal outcomes including cesarean delivery for non-reassuring fetal status, 5-min Apgar score < 7, admission to neonatal intensive care unit, neonatal acidosis, neonatal brain lesion, and use of mechanical ventilation [27]. Consequently, the value of CPR as a single screening parameter to predict operative delivery due to IFC or APO is very limited. In addition, we found that nulliparity, use of oxytocin for augmentation of labor, and BW percentile were independent predictors of operative delivery due to IFC. Therefore, models including placental, maternal, fetal, and intrapartal parameters may improve prognostic accuracy [28–30].

The strengths of this study are the inclusion of a well-defined AGA population and the exclusion of maternal comorbidities or pregnancy complications that could influence the main outcomes. Limitations are the retrospective design of the study, selection bias of a tertiary referral center population, and limited internal validity due to several examiners. In addition, managing obstetricians were not blinded to CPR values. However, low CPR was not a criterion for induction of labor or for the indication of operative delivery due to IFC. Thus, it may not have substantially affected our main results.

In conclusion, in our population, AGA fetuses with low CPR in late-term pregnancies that underwent elective induction of labor showed a higher risk of operative delivery for IFC and no increase in APO. Additionally, the predictive value of CPR for operative delivery due to IFC and APO was poor. Therefore, nowadays, using CPR to monitor AGA late-term pregnancies is debatable. Further prospective randomized studies are warranted to assess the value of CPR in this setting.

Conflict of Interest

The authors declare that they have no conflict of interest.

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