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Using fetal abdominal circumference growth velocity in the prediction of adverse outcome in near-term small-for-gestational-age fetuses

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KEYWORDS: abdominal circumference; fetal biometry; fetal Doppler; growth velocity; pregnancy; SGA

ABSTRACT

Objective *To investigate whether abdominal circumference growth velocity (ACGV) improves the prediction of perinatal outcome in small-for-gestational-age (SGA) fetuses beyond that afforded by estimated fetal weight (EFW) and cerebroplacental ratio (CPR).*

Methods *A cohort of 235 singleton SGA fetuses at 36–38 weeks' gestation was examined. ACGV, EFW and CPR centiles were calculated. ACGV centile was determined using data from a large database of 19–21- and 36–38-week scans in an unselected population. Binary variables of ACGV $< 10^{th}$, EFW $< 3^{rd}$ and CPR $< 5^{th}$ centiles were defined as abnormal. Two composite adverse outcomes (CAO) were explored: CAO-1 defined as at least one of umbilical artery pH < 7.10, 5-min Apgar score < 7 or neonatal unit admission, and CAO-2 that included in addition hypoglycemia, intrapartum fetal distress and perinatal death. Univariate and multivariate logistic regression analyses were performed to analyze the relationship between the three risk factors and their predictive value for CAO. The change in screening performance afforded by adding ACGV to EFW and CPR was assessed and receiver–operating characteristics (ROC) curves were calculated.*

Results *ACGV $< 10^{th}$ centile was an independent risk factor for CAO. The sensitivity, specificity, positive and negative likelihood ratios of a predictive model based on EFW $< 3^{rd}$ centile and CPR $< 5^{th}$ centile were, respectively, 51%, 70%, 1.71 and 0.69 for CAO-1 and 41%, 70%, 1.39 and 0.83 for CAO-2. After addition of ACGV $< 10^{th}$ centile to the model, the respective values were 82%, 46%, 1.54 and 0.38 for CAO-1 and 71%, 47%, 1.34 and 0.62 for CAO-2. Using continuous variables, the areas under the ROC curves improved marginally from 0.669 (95% CI, 0.604–0.729) to 0.741 (95% CI, 0.677–0.798) for CAO-1 and from 0.646 (95% CI, 0.580–0.707) to 0.700 (95% CI, 0.633–0.759) for CAO-2 after addition of ACGV to the model.*

Conclusions *ACGV is a risk factor for adverse neonatal outcome that is independent of EFW and of CPR, although any improvement in the prediction of adverse outcome is not statistically significant. Copyright © 2017 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Stillbirth is a devastating pregnancy outcome occurring in up to 1% of pregnancies in the developed world[1]. Accumulating data suggest that fetal growth restriction (FGR) is a major determinant of perinatal mortality and morbidity[2,3], in particular stillbirth[4,5]. FGR is also associated with an increased risk of adult chronic disease, such as coronary heart disease, stroke, hypertension, non-insulin-dependent diabetes[6] and neurocognitive dysfunction[7].

Small-for-gestational age (SGA), defined as fetal weight/birth weight below the 10th centile for gestational age, is commonly used as a proxy for FGR[8]. However, many SGA fetuses are physiologically small and have reached their appropriate growth potential on the basis of genetic, placental, maternal and environmental factors[9]. Therefore, the interchangeable use of the terms FGR and SGA is incorrect and the ability to detect FGR

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fetuses among the SGA population, and even among the appropriately grown (appropriate-for-gestational age, AGA) population, is important in order to prevent unnecessary intervention and iatrogenic preterm birth.

Multiple markers for FGR have been investigated, including ultrasound, biophysical and even biochemical factors, and integrated into predictive models[10,11]. These studies have demonstrated the predictive value of estimated fetal weight (EFW), uterine artery Doppler and particularly the cerebroplacental ratio (CPR)[10,11]. However, assessment of abdominal circumference growth velocity (ACGV) can also identify SGA neonates at highest risk for adverse outcome[12–14]. Although reduced ACGV is associated with low EFW and CPR[13], it is not clear whether it is independent of these markers and whether it can be used in conjunction with them to improve the prediction of adverse outcome.

The aim of this study was to investigate the relationship of fetal ACGV with EFW and CPR as predictors of perinatal outcome in SGA fetuses and determine whether use of ACGV, in addition to EFW and CPR, improves the prediction of adverse outcome.

METHODS

This was a cohort study conducted at the John Radcliffe Hospital, Oxford, UK, a large teaching hospital with more than 8000 deliveries per annum. Growth scanning in the third trimester of pregnancy was performed according to risk factors and serial measurement of the symphysis–fundal height, as per local and national guidelines[15,16]. Women referred to the Fetal Medicine Unit with a singleton pregnancy diagnosed antenatally as SGA (EFW < 10th centile using Hadlock charts[17]) from 36 + 0 weeks' gestation were eligible for inclusion. Exclusion criteria were multiple pregnancy, abnormal karyotype, missing data on first-trimester dating, and life-limiting fetal abnormalities or those requiring neonatal surgery. The scan performed between 36 + 0 and 38 + 0 weeks' gestation for each fetus was included in the analysis.

Gestational age (GA) was confirmed based on first-trimester crown–rump length (CRL) at the time of the nuchal scan[18]. Fetal biometry was measured according to INTERGROWTH-21st standards[19]. Umbilical artery (UA) pulsatility index (PI) was calculated from a free-floating portion of the umbilical cord. Middle cerebral artery (MCA)-PI was measured in a transverse view of the fetal head, at the level of its origin from the circle of Willis[20], and the CPR was calculated as the ratio MCA-PI/UA-PI[21]. Doppler recordings were performed according to the 'Doppler quality criteria' used in the INTERGROWTH-21st Project[19].

ACGV centiles for this cohort were calculated using, as a reference range, data from a large unselected population of 3334 fetuses followed at this unit, obtained after the introduction of a routine 36-week growth scan. These data were extracted and modelled separately for 19–21 and 36–38 weeks in order to produce locally fitted *Z*-scores. The ACGV was defined as the *Z*-score difference between the 19–21- and 36–38-week scans, divided by the interval in days between the two ultrasound evaluations and multiplied by 100[22]. The EFW was expressed as a centile according to Hadlock *et al.*[17]. The CPR was expressed as a centile for gestational age according to Baschat–Gembruch charts[21]. Established cut-offs of EFW[23], ACGV[22] and CPR[21] were used.

All ultrasound examinations were performed by two experienced operators (A.C. or M.V.) using a Voluson E8 (GE Medical Systems, Zipf, Austria) machine, equipped with a 6–2-MHz linear curved-array transducer. Both sonographers underwent training and performed standardization exercises. Their performance was also monitored by a comprehensive package of quality control for ultrasonographic data collection in fetal biometry according to the INTERGROWTH-21st Project[24].

Pregnancies with EFW < 10th centile were either delivered or managed conservatively with close follow-up, as described elsewhere[23]. Composite adverse outcome 1 (CAO-1) was defined, in accordance with a recent paper demonstrating the value of ACGV as a predictor of adverse outcome[12], as one or more of the following criteria: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to the neonatal unit. A second composite adverse outcome (CAO-2) also included hypoglycemia (blood glucose < 2.5 mmol/L), intrapartum fetal distress requiring expedited delivery and perinatal death.

Data were collected prospectively from the hospital electronic database of ultrasonography (ViewPoint, GE Healthcare), electronic patient record (Cerner Millennium, London, UK) and electronic record system for neonatal unit care (Badgernet, Clevermed, Edinburgh, UK), and merged postnatally.

Univariate logistic regression analysis using continuous and binary variables was performed as a preliminary analysis to establish which of the adverse outcome measures were related significantly to ACGV, EFW and CPR. Simple correlation confirmed that there is no problem of co-linearity with these predictors. Multivariate simultaneous entry logistic regression analysis was then performed, using as binary variables the three considered predictors: ACGV < 10th centile, EFW < 3rd centile and CPR < 5th centile. For each outcome, the regression model included the factors that were significant predictors in univariate analysis.

In order to determine the performance of ACGV in predicting adverse outcome, three combinations of predictors were analyzed: (1) EFW with CPR, (2) ACGV alone, and (3) EFW, CPR and ACGV together. Initially these were analyzed as continuous variables, using a statistical model to calculate the probability of developing adverse outcome[25]. For this purpose, binary logistic regression analysis was performed using each target predictor for each adverse outcome. The intercept and regression coefficient for each variable were obtained. The following equation was then used to calculate the risk of adverse outcome[25]: Fetus risk = exp(fetus risk score)/[1 + exp(fetus risk score)] × 100, where fetus

risk score = intercept + (regression coefficient variable$_1$ × variable$_1$) + (regression coefficient variable$_n$ × variable$_n$). Areas under the receiver–operating characteristics curves (AUC) with 95% CI were calculated.

The three predictors were then analyzed as binary variables for clinical applicability. These were: (1) EFW < 3rd centile or CPR < 5th centile, (2) ACGV < 10th centile of the reference range (ACGV < −1.3091) alone, and (3) EFW < 3rd centile or CPR < 5th centile or ACGV < 10th centile. The sensitivity and specificity were calculated, with positive and negative likelihood ratios (LRs), for all adverse outcomes. Percentage occurrence or measures of central tendency were calculated for all variables of interest.

Table 1 Baseline characteristics of 235 women with small-for-gestational-age (SGA) fetus at 36–38 weeks' gestation included in study cohort

Characteristic	*Value*
Maternal age (years)	29.8 ± 5.99
Body mass index	
< 18.5 kg/m^2	17 (7.2)
18.5–24.9 kg/m^2	132 (56.2)
25.0–29.9 kg/m^2	58 (24.7)
30.0–34.9 kg/m^2	23 (9.8)
35.0–39.9 kg/m^2	4 (1.7)
> 40 kg/m^2	1 (0.4)
Nulliparous	115 (48.9)
Maternal ethnicity	
Caucasian	163 (69.4)
Afro-Caribbean	4 (1.7)
Asian	36 (15.3)
Mixed	32 (13.6)
Cigarette smoker	45 (19.1)
Alcohol abuse	3 (1.3)
Drug abuse	9 (3.8)
Essential hypertension	8 (3.4)
Pre-eclampsia	14 (6.0)
Prepregnancy disease	100 (42.6)
Diabetes (Type 1 or Type 2)	0 (0)
Gestational diabetes	15 (6.4)
Previous stillbirth	3 (1.3)
Previous SGA	60 (25.5)
In-vitro fertilization pregnancy	12 (5.1)

Data are presented as mean ± SD or *n* (%).

Table 2 Delivery characteristics, pregnancy outcome and ultrasound measurements at 36–38 weeks of 235 small-for-gestational-age fetuses included in study cohort

Parameter	*Value*
GA at delivery (days)	267 ± 9.04
Induction of labor	135 (57.4)
Delivery mode	
Spontaneous vaginal delivery	140 (59.6)
Instrumental vaginal delivery	26 (11.1)
Elective Cesarean section	32 (13.6)
Emergency Cesarean section	37 (15.7)
Neonatal sex	
Female	131 (55.7)
Male	104 (44.3)
Birth weight (g)	2481 ± 342.31
Birth weight < 10th centile*	163 (69.4)
Birth-weight centile*	2.69 ± 1.32
Fetal hypoglycemia†	26 (11.1)
5-min Apgar score < 7	2 (0.9)
Arterial cord pH < 7.10	3 (1.3)
Neonatal unit admission	32 (13.6)
Perinatal mortality	1 (0.4)
Composite adverse outcome 1‡	35 (14.9)
Composite adverse outcome 2§	71 (30.2)
EFW at third-trimester scan (g)	2262 ± 206
EFW < 3rd centile¶	51 (21.7)
CPR	1.76 ± 0.54
CPR < 5th centile¶	45 (19.1)
ACGV**	−1.163 ± 1.05
ACGV < 10th centile**	93 (39.6)

Data are presented as mean ± SD or *n* (%). *Birth-weight centile calculated using growth charts generated by INTERGROWTH-21st Project[26]. †Hypoglycemia defined as neonatal blood glucose < 2.5 mmol/L. ‡Composite adverse outcome 1 defined in accordance with definition used in POP study[12] as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. §Composite adverse outcome 2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery (instrumental vaginal delivery or emergency Cesarean section for fetal distress) and perinatal death. ¶Estimated fetal weight (EFW) expressed as centile for gestational age (GA) according to Hadlock *et al.*[17]; cerebroplacental ratio (CPR) expressed as centile for GA according to Baschat–Gembruch charts[21]. **Abdominal circumference growth velocity (ACGV) defined as *Z*-score difference between 19–21- and 36–38-week scans, divided by interval in days between the two ultrasound evaluations and multiplied by 100; 10th centile of change in *Z*-score calculated using, as reference range, data from a large unselected population (*n* = 3334 fetuses) at John Radcliffe Hospital, Oxford, UK[22].

Table 3 Univariate logistic regression analysis for prediction of composite adverse outcome (CAO)-1 and CAO-2 in near-term small-for-gestational-age fetuses based on continuous variables abdominal circumference growth velocity (ACGV), estimated fetal weight (EFW) and cerebroplacental ratio (CPR) centiles, and binary variables ACGV < 10th centile, EFW < 3rd centile and CPR < 5th centile

	Odds ratio (95% CI)					
Outcome	*ACGV centile*	*EFW centile*	*CPR centile*	*ACGV < 10th centile*	*EFW < 3rd centile*	*CPR < 5th centile*
CAO-1	2.02 (1.41–2.90)***	1.00 (1.00–1.01)***	1.02 (1.01–1.04)**	2.45 (1.15–5.21)*	2.52 (1.17–5.45)*	3.03 (1.38–6.63)**
CAO-2	1.68 (1.26–2.24)***	1.00 (1.001–1.004)**	1.02 (1.01–1.03)**	2.00 (1.12–3.57)*	1.35 (0.70–2.60)	2.45 (1.25–4.78)**

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. CAO-1 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. CAO-2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery and perinatal death.

Statistical analysis was carried out using SPSS version 22 (IBM Corp., Armonk, NY, USA). Institutional review board approval was obtained (27 July 2017, REC 17/SC/0374).

RESULTS

A total of 249 women with a singleton pregnancy attended the Fetal Medicine Unit at John Radcliffe Hospital between October 2014 and July 2016, having had a scan showing an EFW $< 10^{th}$ centile between $36+0$ and $38+0$ weeks. Of these, five women were excluded because of fetal abnormality, three because remeasurement showed EFW to be $> 10^{th}$ centile and six because follow-up data were not obtainable. Therefore, 235 pregnancies diagnosed as SGA were examined. Maternal baseline characteristics are shown in Table 1.

Mean gestational age of the study cohort was 256.8 ± 4.67 days. Mean interval between the third-trimester ultrasound scan and delivery was 10.3 ± 12 days. Mean EFW of the study cohort was 2262 ± 206 g and 51 (21.7%) cases had EFW $< 3^{rd}$ centile. At birth, 163 (69.4%) fetuses were SGA according to the INTERGROWTH-21st Project charts[26]. Pregnancy outcomes and ultrasound parameters of the study cohort are shown in Table 2.

There was a significant but not strong correlation between the ACGV and EFW centiles ($r = 0.25$, $P = 0.001$) and between the ACGV and CPR centiles ($r = 0.22$, $P = 0.001$). Univariate analysis using ACGV, EFW and CPR centiles as continuous variables showed that all three markers predicted significantly both CAO-1 and CAO-2 in near-term SGA fetuses. All three binary variables, EFW $< 3^{rd}$ centile, CPR $< 5^{th}$ centile and ACGV $< 10^{th}$ centile, were associated significantly with both outcomes on univariate analysis, except for EFW $< 3^{rd}$ centile, which did not predict significantly CAO-2 (Table 3).

Multivariate simultaneous entry logistic regression analysis using as binary variables all risk factors that were significant predictors of adverse outcome on univariate analysis showed that only CPR $< 5^{th}$ centile [adjusted OR (aOR) 2.54 (95% CI, 1.07–5.99)] was a significant predictor of CAO-1. For CAO-2, both CPR $< 5^{th}$ [aOR 2.42 (95% CI, 1.18–4.99)] and ACGV $< 10^{th}$ centile [aOR 1.95 (95% CI, 1.07–3.54)] were significant predictors (Table 4).

The principal benefit of using ACGV in addition to EFW and CPR for the prediction of adverse outcome in SGA fetuses is the improvement of the negative likelihood ratios (LR−) (Table 5). For CAO-1, LR− was 0.69 (95% CI, 0.49–0.99) for EFW $< 3^{rd}$ centile or CPR $< 5^{th}$ centile, improving to 0.38 (95% CI, 0.18–0.80) when ACGV $< 10^{th}$ centile was included. For CAO-2, the corresponding LR− values were 0.83 (95% CI, 0.67–1.04) and 0.62 (95% CI, 0.41–0.93).

AUCs of the three logistic regression models are shown in Table 6 and receiver–operating characteristics curves for both outcomes are shown in Figure 1. At a 50% specificity, corresponding to approximately 50% of SGA fetuses being labelled as 'high risk', the addition of ACGV to EFW and CPR increased the sensitivity for CAO-1 from 71.43% (95% CI, 53.7–85.4) to 78.79% (95% CI, 61.1–91.0), and for CAO-2 from 68.57% (95% CI, 56.4–79.1) to 75.76% (95% CI, 63.6–85.5).

Table 4 Simultaneous entry logistic regression analysis for prediction of composite adverse outcome (CAO)-1 and CAO-2 in near-term small-for-gestational-age fetuses based on binary variables estimated fetal weight (EFW) $< 3^{rd}$ centile, cerebroplacental ratio (CPR) $< 5^{th}$ centile and abdominal circumference growth velocity (ACGV) $< 10^{th}$ centile

Outcome	*Predictor*	*Wald test*	*Adjusted OR (95% CI)*	P
CAO-1	EFW $< 3^{rd}$ centile	2.49	1.95 (0.85–4.48)	0.115
	CPR $< 5^{th}$ centile	4.50	2.54 (1.07–5.99)	0.034
	ACGV $< 10^{th}$ centile	3.68	2.15 (0.98–4.68)	0.055
CAO-2	CPR $< 5^{th}$ centile	5.75	2.42 (1.18–4.99)	0.016
	ACGV $< 10^{th}$ centile	4.77	1.95 (1.07–3.54)	0.029

CAO-1 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. CAO-2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery and perinatal death. OR, odds ratio.

DISCUSSION

In this paper we demonstrate that in near-term fetuses diagnosed antenatally as SGA, a reduction ($< 10^{th}$ centile) in ACGV between 20 and 36 weeks is a risk factor for adverse outcome that is independent of EFW and CPR. The increase in the AUC when ACGV is added to the model is nevertheless not statistically significant. Our findings suggest, but do not prove, that using ACGV in addition to EFW and CPR will improve risk stratification of near-term SGA fetuses.

The detection of SGA has been a traditional cornerstone of antenatal care. The DIGITAT study[27] and a subsequent Cochrane review[28] concluded that there is no difference in terms of perinatal outcome between systematic induction of delivery at term *vs* expectant management in SGA fetuses, although the studies were underpowered for stillbirth. Many guidelines consequently recommend expedited delivery from 37 or 38 weeks in pregnancies in which the EFW is $< 10^{th}$ centile irrespective of Doppler indices or the absence of pregnancy complications[8,29].

The limitations of this practice are increasingly appreciated. As SGA is just one manifestation of FGR, even the universal detection of SGA will have limited effects on stillbirth and neonatal morbidity[30,31]. As some SGA fetuses are constitutionally small[32], and probably not at increased perinatal risk, iatrogenic delivery may be harmful[23]. It is therefore important to identify other predictors of adverse outcome. The most studied predictor is the CPR, which predicts adverse neonatal outcome in both SGA and AGA fetuses[13,33–35], although this is dependent on the interval between measurement

Table 5 Diagnostic performance of three different predictive models based on estimated fetal weight (EFW), cerebroplacental ratio (CPR) and abdominal circumference growth velocity (ACGV), expressed as binary variables, for the prediction of composite adverse outcome (CAO)-1 and CAO-2 in near-term small-for-gestational-age fetuses

Predictive model	n *(%)*	*Sensitivity (%) (95% CI)*	*Specificity (%) (95% CI)*	*PPV (%) (95% CI)*	*NPV (%) (95% CI)*	*LR+ (95% CI)*	*LR− (95% CI)*
CAO-1	35 (14.9)						
EFW < 3rd centile or CPR < 5th centile	17 (48.6)	51.43 (33.99–68.62)	69.90 (62.95–76.23)	23.38 (17.17–30.98)	88.96 (84.99–91.98)	1.71 (1.16–2.51)	0.69 (0.49–0.99)
ACGV < 10th centile	20 (57.1)	60.61 (42.14–77.09)	61.38 (54.04–68.35)	21.51 (16.47–27.56)	89.92 (85.20–93.26)	1.57 (1.13–2.18)	0.64 (0.41–0.99)
EFW < 3rd centile or CPR < 5th centile or ACGV < 10th centile	27 (77.1)	82.35 (65.47–93.24)	46.35 (39.15–53.68)	21.37 (18.15–25.00)	93.68 (87.60–96.89)	1.54 (1.25–1.88)	0.38 (0.18–0.80)
CAO-2	71 (30.2)						
EFW < 3rd centile or CPR < 5th centile	27 (38.0)	41.43 (29.77–53.83)	70.19 (62.48–77.13)	37.66 (29.53–46.55)	73.38 (68.84–77.47)	1.39 (0.96–2.00)	0.83 (0.67–1.04)
ACGV < 10th centile	36 (50.7)	53.73 (41.12–66.00)	63.23 (55.12–70.82)	38.71 (31.80–46.10)	75.97 (70.40–80.78)	1.46 (1.08–1.98)	0.73 (0.55–0.97)
EFW < 3rd centile or CPR < 5th centile or ACGV < 10th centile	46 (64.8)	70.59 (58.29–81.02)	47.47 (39.48–55.55)	36.64 (31.84–41.72)	78.95 (71.48–84.88)	1.34 (1.09–1.66)	0.62 (0.41–0.93)

CAO-1 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. CAO-2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery and perinatal death. LR+/−, positive/negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Table 6 Area under the receiver–operating characteristics curve (AUC) and sensitivity at 50% and 90% specificity of three logistic regression models based on estimated fetal weight (EFW), cerebroplacental ratio (CPR) and abdominal circumference growth velocity (ACGV), expressed as continuous variables, for the prediction of composite adverse outcome (CAO)-1 and CAO-2 in near-term small-for-gestational-age fetuses

	CAO-1			*CAO-2*		
		Sensitivity (%) (95% CI) at:			*Sensitivity (%) (95% CI) at:*	
Model	*AUC (95% CI)*	*50% specificity*	*90% specificity*	*AUC (95% CI)*	*50% specificity*	*90% specificity*
EFW + CPR	0.669 (0.604–0.729)*	71.43 (53.7–85.4)	31.43 (16.9–49.3)	0.646 (0.580–0.707)†	68.57 (56.4–79.1)	25.71 (16.0–37.6)
ACGV	0.692 (0.627–0.752)	75.76 (57.7–88.9)	42.42 (25.5–60.8)	0.644 (0.577–0.707)	70.15 (57.7–80.7)	29.85 (19.3–42.3)
EFW + CPR + ACGV	0.741 (0.677–0.798)*	78.79 (61.1–91.0)	42.42 (25.5–60.8)	0.700 (0.633–0.759)†	75.76 (63.6–85.5)	37.88 (26.2–50.7)

*AUC for EFW + CPR *vs* AUC for EFW + CPR + ACGV: $P = 0.11$. †AUC for EFW + CPR *vs* AUC for EFW + CPR + ACGV: $P = 0.15$. CAO-1 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. CAO-2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery and perinatal death.

and delivery[36]. EFW < 3rd centile[37], uterine artery Doppler[38,39] and biochemical markers such as placental growth factor[40] have also been used.

Algorithms for the prediction of adverse outcome in fetuses diagnosed as SGA near term have been proposed[11,41]. An adaptation of these that includes pregnancy-induced hypertension improves neonatal morbidity in SGA fetuses[23], demonstrating the need for better risk stratification.

In addition, fetal growth velocity appears to play an important role. Both SGA and AGA fetuses with slow velocity have higher risks of preterm birth and longer neonatal unit admissions than those with normal growth[42]. Sovio *et al.*[12] used the difference between *Z*-scores of abdominal circumference (AC) measurements at 20 weeks and the third trimester in unselected nulliparous women, with non-revealed results. The lowest decile of ACGV detected the fetuses at highest risk of adverse outcome. Indeed if growth velocity was normal, an EFW < 10th centile was not significantly associated with adverse neonatal outcome.

Khalil *et al.*[13] demonstrated that a low CPR is indeed associated with reduced growth velocity, in both AGA and SGA fetuses. Among fetuses that were SGA and had a low CPR, 31% had an ACGV < 10th centile, whereas the figure was 16.1% when the CPR was normal. Nevertheless, 7.9% of AGA fetuses also had a low ACGV, suggesting that most fetuses with a low ACGV were neither SGA nor had a low CPR.

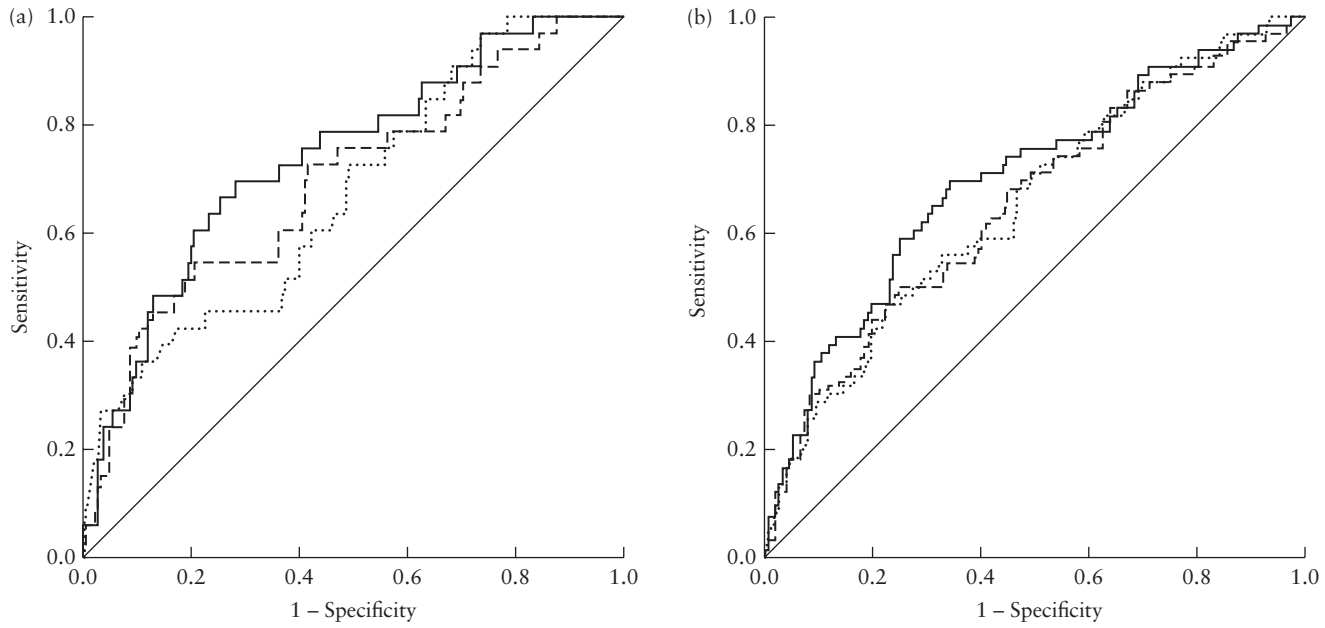

Figure 1 Receiver–operating characteristics curves of three logistic regression models based on estimated fetal weight (EFW), cerebroplacental ratio (CPR) and abdominal circumference growth velocity (ACGV), expressed as continuous variables, for prediction of composite adverse outcomes 1 (a) and 2 (b) in near-term small-for-gestational-age fetuses. Composite adverse outcome 1 defined in accordance with definition used in POP study[12] as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7 and admission to neonatal unit. Composite adverse outcome 2 defined as at least one of: umbilical artery pH < 7.10, 5-min Apgar score < 7, admission to neonatal unit, hypoglycemia, intrapartum fetal distress requiring expedited delivery (instrumental vaginal delivery or emergency Cesarean section for fetal distress) and perinatal death. ——, EFW + CPR + ACGV; – – –, ACGV; ·····, EFW + CPR.

Caradeux *et al.*[43] analyzed growth velocity of the EFW, as opposed to AC, in 472 SGA fetuses in the third trimester and found that fetuses with the lowest growth velocity were at slightly increased risk; however, this risk factor did not predict adverse outcomes better than existing models using EFW, CPR and uterine artery Doppler.

In accordance with Khalil *et al.*[13], we found a significant correlation between ACGV and CPR, as well as EFW. We demonstrated that the growth velocity of the AC, determined from 20 weeks, is nevertheless an independent risk factor and, at least in fetuses thought to be SGA, using ACGV in addition to EFW $< 3^{rd}$ and CPR $< 5^{th}$ centile might improve the prediction of adverse outcome in SGA fetuses.

Whilst the specificity of our method is poor (Tables 5 and 6), in this high risk group of fetuses, sensitivity is more important than specificity, as routine delivery is the usual default[8,29], and up to 50% of SGA fetuses are considered to show FGR[44]. This approximates to the specificities of the combination of all risk factors as binary variables.

We acknowledge some limitations of this study. Data on undiagnosed SGA fetuses were not available, sample size was small and the confidence intervals overlapped meaning that although ACGV is an independent risk factor, we cannot be confident that it improves screening performance. In addition, the outcomes explored were subject to other antepartum and intrapartum factors and to intervention, and therefore there is a potential 'treatment paradox'. The ACGV calculation uses only two points and its usage is limited by difficulties in quantification because of the complex methodology required for its calculation, a problem that is surmountable using automated software. Finally, we did not collect data on third-trimester uterine artery, a tool that might add further sensitivity for risk stratification of SGA fetuses[11].

We did not consider fetuses that were not SGA. Whilst both ACGV[12] and CPR[9] may be important in AGA fetuses, it is likely that the screening performance in this group, even when using all our risk factors, is still poor. AGA fetuses account for more stillbirths than SGA ones, and it is in this group that specificity matters so that over-intervention is prevented. Ultimately, adverse perinatal events will be best predicted by modeling all independent risk factors as continuous variables.

In conclusion, estimation of fetal weight in the third trimester is an inadequate screening test for adverse perinatal outcome. Expediting delivery of all small fetuses, an increasing and widely recommended practice, should be restricted to those with risk factors. Our data suggest that a reference range of ACGV from 20 weeks should be incorporated in risk stratification.

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