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Prenatal prediction of adverse outcome using different charts and definitions of fetal growth restriction

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CONTRIBUTION

What are the novel findings of this work?

With uniformly low sensitivities, neither prescriptive nor descriptive charts improve performance of various FGR definitions. At multivariate logistic regression, Uterine artery Doppler and EFW below the 5th centile were the only parameters to be consistently associated with adverse outcome irrespective of definitions or growth references used.

What are the clinical implications of this work?

The choice of different definitions and/or growth charts does not allow to distinguish between normal and pathological fetal growth. The use of an individual ultrasound parameter such as EFW or Doppler indices is complicated due to close correlation. This information is likely to improve the identification of pregnancies at risk of adverse events.

ABSTRACT

Objective: Fetal growth assessment by ultrasound aims to identify small babies that are at higher risk of perinatal morbidity and mortality. The current study explores if the association between suboptimal fetal growth and adverse perinatal outcome varies with different definitions of fetal growth restriction and weight charts/standards.

Methods: This was a retrospective cohort study of 17261 singleton non-anomalous pregnancies from 24^{+0} weeks' gestation at a tertiary referral hospital. Estimated fetal weight (EFW) and Doppler indices were converted into gestational age specific centiles using a growth reference standard (Intergrowth-21) and various reference charts (Hadlock, Fetal Medicine Foundation [FMF] and Swedish). Test characteristics were assessed using definitions of FGR according to the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), Society of Maternal and Fetal Medicine (SMFM) and Swedish criteria. Adverse perinatal outcome was defined as perinatal death, admission to the neonatal intensive care (NICU) at term, 5' Apgar score < 7, and therapeutic cooling for neonatal encephalopathy. The association between FGR according to different definitions and adverse perinatal outcome was compared. Multivariate logistic regression was used to investigate the strength of the associations between ultrasound parameters and adverse perinatal outcome. Ultrasound parameters were also tested for correlation.

Results: Intergrowth-21 (IG-21), Hadlock and FMF fetal size references classified 1.47%, 3.55% and 4.5% fetuses respectively as FGR using the ISUOG definition and 2.87%, 8.82% and 10.6% fetuses respectively using the SMFM definition. The sensitivity of each of the definition/chart combinations for adverse perinatal outcome varied from 4.4% (ISUOG definition with IG-21 charts) to 13.2% (SMFM definition with FMF charts). The concomitant specificity also varied from 89.4% (SMFM definition with FMF charts) to 98.6% (ISUOG definition with IG-21 charts). ISUOG and Swedish criteria showed the highest specificity, positive predictive value, and positive likelihood ratio in detecting adverse outcomes irrespective of which fetal size reference charts/standards were used. Conversely, the SMFM definition had the highest sensitivity across all investigated growth charts. Low estimated fetal weight, elevated uterine artery mean PI, abnormal umbilical artery PI and abnormal cerebro-placental ratio were all significantly associated with adverse perinatal outcome and there was positive correlation between the covariates. Multivariate logistic regression showed that uterine artery Doppler mean PI and smallness (EFW below the 5^{th} centile) were the only parameters to be consistently associated with adverse outcome irrespective of definitions or fetal size growth charts used.

Conclusions: The prevalence of FGR is variable based on the specific definition as well as the fetal size reference chart used to diagnose FGR. Irrespective of the method of classification, the sensitivity for the identification of adverse perinatal outcome remains low. Estimated fetal weight, uterine artery and fetal Dopplers are all significant predictors of adverse perinatal outcome. As these indices are correlated to each other, a prediction algorithm is advocated to overcome the limitations of using them in isolation.

INTRODUCTION

Fetal growth restriction (FGR) is known to be associated with a significant burden of perinatal mortality and morbidity[1]. Over the years, efforts have been put into prenatal detection of fetal smallness with significant variations in size thresholds used and detection rates[2,3]. Antenatal assessment of fetal size using ultrasound (US) has been the primary modality to identify growth abnormalities. Estimated fetal weight (EFW) below the 10th centile is referred to as 'FGR or 'small for gestational age' (SGA) according to the American College of Obstetrics and Gynecology[4], a definition adopted by the Society for Maternal and Fetal Medicine (SMFM)[5]. Although smallness alone is not necessarily sufficient for the term FGR according to the consensus definition[6], it is an integral component to qualify the diagnosis. Performances of FGR definitions have been compared in predicting as main outcome a low birthweight[7]. However smallness is not a disease itself: it can be due to physiological variation, or it can be the result of an altered intrauterine environment (FGR). The distinction between the two is challenging and size alone is of limited aid as a proxy for growth potential. Moreover, weight centiles vary greatly according to the chart used for a given EFW[8,9].

The pregnancy outcome prediction (POP) study[10] reported smallness alone had limited sensitivity for neonatal morbidity. The threshold used could explain this. It may also be because of the use of a specific size standard to assess the extent of deviation from the expected size. Birthweight is unknown till the baby is born. Therefore, it is not appropriate to use it as a predictor for morbidity or to use it to decide on intervention to avoid it. Birthweight is influenced by gestational age at delivery and preterm births pose an unsolvable bias in creating optimal references[11]. Therefore EFW rather than birthweight is a more appropriate measure to mandate intervention.

We sought to compare the extent of association between FGR and adverse perinatal outcome, using several definitions and weight charts/standards. We also investigated which individual biometric and/or functional ultrasound parameter/s are associated with perinatal mortality and morbidity.

METHODS

Study design and cohort

This is a single-centre historical cohort study in a tertiary referral hospital. Cases were identified among women who attended for antenatal US examinations at St George's University Hospital between April 2016 and March 2022. Since all pregnant women at St George's Hospital are offered a routine ultrasound examination between 36-37 weeks of gestation, the population comprises both high and low risk pregnancies. When EFW is noted to be < 10th centile, serial growth scans are arranged. Induction of labor is offered from 37 weeks for EFW <5th centile, and from 39 weeks for EFW <10th centile. US data were extracted from the departmental database (ViewPoint version 5.6.26.148, ViewPoint Bildverarbeitung GmbH, Wessling, Germany) and the maternity registry (EuroKing, Wellbeing Software, Mansfield, UK).

Inclusion criteria were singleton pregnancies from a gestational age of 24^{+0} weeks onwards, with no evidence of fetal structural or chromosomal abnormality and known birth outcome. Gestational age was assigned at a dating scan in the first trimester using crown-rump length measurement according to NICE guidelines[12]. Multiple pregnancies, pregnancies with known fetal abnormality or with missing outcome data were excluded. We also excluded multiple examinations in the same pregnancy. The examination closest to the date of delivery was retained. Details retrieved comprised: maternal characteristics (age, body mass index, parity and ethnicity), ultrasound parameters (fetal biometry, uterine artery, umbilical artery, middle cerebral artery Dopplers indices) and birth outcomes (gestational age at delivery, birthweight, gender, Apgar score, admission to neonatal intensive care unit, therapeutic cooling for neonatal encephalopathy).

Ultrasound measurements were obtained according to ISUOG guidelines[13]. EFW was calculated using the formula of Hadlock[14]. Centiles for EFW and abdominal circumference (AC) centiles were then calculated according to both reference standard (Intergrowth-21[15,16]) and reference charts (Hadlock[17], FMF[18]). For the Swedish[19] criterion for the term SGA, the EFW was calculated according to the formula developed by Persson and Weldner[20]. Deviation of the EFW greater than 22% from expected weight was used to identify SGA fetuses, as previously described[21,22]. Of note, this criterion mainly identifies severe SGA since the lowest 10th centile equals to a weight deviation of less than 16.5%.

Uterine artery Doppler (UtAD) pulsatility index (PI) on the left and right side were averaged and was considered abnormal if it exceeded the 95th centile according to reference ranges by

Gòmez et al[23]. Intergrowth-21[24] (IG-21) and FMF reference ranges[25] were used to assess the umbilical artery (UA) PI, the middle cerebral artery (MCA) PI and the cerebroplacental ratio. These were considered abnormal if >95th centile and <5th centile respectively)[25]. Other Doppler references were compared for late FGR definition according to ISUOG[26,27].

Low birthweight by itself, is not an adverse event and was therefore not included as an outcome. In the current study, adverse outcome (AO) was defined as: stillbirth, neonatal death, admission to neonatal intensive care (NICU) at term, low Apgar score at 5 minutes (< 7) or therapeutic cooling for neonatal encephalopathy (NE)[10].

Statistical analysis

Sensitivity, specificity, positive and negative predictive value (PPV, NPV), positive and negative likelihood ratios (LR) were compared for ISUOG[6], SMFM[5] and Swedish[21] definitions. Multivariate logistic regression analysis was applied for four potential predictors of adverse outcome: smallness (EFW <5th centile) , abnormal PI of Uterine arteries, umbilical artery or cerebroplacental ratio. Since umblical artery PI and cerebro-placental ratio (CPR) are highly likely to be correlated introducing multi-collinearity, we performed a Pearson correlation test to check this hypothesis and then two logistic regression analyses with predictors that included either umbilical artery PI or CPR. Since results were comparable with the two fetal Doppler indices, we chose to include only CPR in multivariate logistic regression analysis. Statistical analysis was performed using SPSS v 28.0, IBM Corp., Armonk, NY, USA. Data were reported as median and interquartile range for continuous variables and in numbers and percentages for categorical variables.

Confirmation was obtained from the ethics committee that formal ethical approval was not required for this retrospective study that utilized routinely collected data.

RESULTS

Among 19084 pregnancies over the 8-year period, 17261 pregnancies met the inclusion criteria and 521 (3%) experienced at least one of the composite adverse outcomes (Figure 1). Individual adverse outcomes are shown in supplementary material (Table S1). The choice of only term NICU admissions in composite adverse perinatal outcomes (CAPO) makes our cohort representative of the most severe AO related solely to FGR in term pregnancies. As shown in Figure 1, only a minority of FGR suspected pregnancies (irrespective of definitions and charts) experienced AO. Population characteristics are shown in Table 1. The cohort was represented mainly by nulliparous and of white ethnicity women (52% and 65.3% respectively), both variables were significantly more prevalent in the AO subcohort. Significant differences were seen in birthweight centiles, and centiles of maternal and fetal Doppler parameters on univatiate analyses. The prevalence of FGR varied in our cohort with different definitions and growth charts (Figure 1 and Table 2). The prevalence of FGR identified by ISUOG definition was 1.47%, 3.55% and 4.5% according to Intergrowth, Hadlock and FMF growth charts respectively. Results are presented for all cases identified by ISUOG definition, while separate analyses for early vs late FGR are available in Table S2. Furthermore, other Doppler reference charts were considered and showed comparable results for late FGR figures (Table S3). SMFM criteria categorised 2.87%, 8.82% and 10.6% of the fetuses in the study population as growth restricted. Swedish definition, comprising a ≤−22% deviation from EFW references, identified 1.87% of fetuses as abnormally small. Overall, descriptive growth charts (Hadlock, FMF and Swedish) classified more fetuses as growth restricted than prescriptive Intergrowth-21 antenatal standards.

The performance of EFW charts in detecting FGR associated with adverse outcome is shown in Table 2. Median sensitivity was 7.68%, ranging from 4.4% (ISUOG definition applied to IG-21 charts) to 13.2% (SMFM definition applied to FMF charts). Median specificity was 96.6%, from 89.4% (SMFM definition applied to FMF charts) to a maximum of 98.6% (ISUOG definition applied to IG-21 charts).

Irrespective of growth charts used, ISUOG and Swedish criteria showed the highest specificity, positive predictive value and likelihood ratio in detecting adverse outcomes among SGA fetuses. Conversely, SMFM definition had the highest sensitivity. Negative predictive values and likelihood ratios were similar across all definitions of SGA.

Several ultrasound indices (EFW, abnormal UA PI above the 95th centile, abnormal CPR below the 5th centile and abnormal UtAD above the 95th centile) were explored for association with adverse perinatal outcomes among the population. In order to explore multi-collinearity

between abnormal umbilical artery PI, middle cerebral artery PI and cerebro-placental ratio, Spearman's test was performed (Table 4). It showed moderate correlation (R = 0.408 , p<0.0005) between abnormal UA PI and CPR, thus logistic regression was performed including only CPR Doppler index. Regarding EFW, different centile charts were considered, with results shown in Table 3 and Figure 2. Overall, multivariate logistic regression analysis identified abnormal uterine artery Dopplers and EFW below the 5th centile as significant independent predictors of adverse outcome irrespective of reference charts used. Uterine Artery Doppler brought independent contribution to outcome prediction among all charts investigated, with a probability uniformly <0.05 and aOR ranging from 1.523 to 1.749 (Table 3). Finally, even greater significance was found for EFW below the 5th centile across the four growth charts analyzed (aOR from 1.545 to 5.576), as shown in Table 3. Conversely, Fetal Dopplers did not consistently reach significance. Only when considering Hadlock and FMF charts, CPR index reached significance with aOR of 1.574 (95% CI, 1.038 – 2.385; p<0.05) and aOR 1.583 (95% CI, 1.051 – 2.383; p<0.05) respectively. When considering IG-21 and Malmo charts, results show an aOR of 1.186 (95% CI, 0.756 – 1.86; p= 0.457) for the former and an aOR of 1.442 (95% CI, 0.947 – 2.197; p= 0.088) for the latter respectively. Table 4 shows the correlation between ultrasound parameters. All the studied parameters show significant correlation. This explains why the ultrasound parameters were highly significant in univariate analysis, but the significance becomes inconsistent with logistic regression analysis.

DISCUSSION

Identifying FGR pregnancies is a key element of antenatal programs aimed at reducing perinatal morbidity and mortality. The outcome 'low birthweight' is commonly used as a proxy for poor growth in utero[28]. Several cut-offs have been compared over the years[29]. Yet, there is no consensus on how to distinguish between normal and pathological fetal growth, the latter associated with adverse perinatal outcome[30,31]. In our cohort, the less stringent SMFM criteria doubled the numbers of 'FGR' fetuses in comparison to ISUOG definition. Nevertheless, the sensitivity remained uniformly low regardless of the chosen definition. These results align with previous finding by Roeckner et al.[7] who showed sensitivities of 10.1% (ISUOG) and 15.1% (SMFM) in predicting composite AO. The Authors included 1054 pregnancies and found a prevalence of 5.2 % for AO compared to 3% in this study. The difference is most likely due to the chosen definition of 'adverse perinatal outcome'. Roeckener et al. included all neonatal unit admissions, as compared to only term neonatal unit admission in the current study. In 2022, Schreiber et al. compared definitions performances for composite severe neonatal morbidity, with similarly disappointing sensitivity for both SMFM and consensus criteria of FGR (8.4% and 4.9% respectively)[32]. Composite severe neonatal morbidity was seen in 17.8% of the 18000 births designated as non-FGR and 31.8% of 'late FGR'. This high prevalence was driven mainly by hypoglycaemia.

We also showed that the sensitivity of FGR definitions is low irrespective of different growth charts. The nuances between prescriptive and descriptive charts are known to give rise to variable detection rates of 'FGR' even in the same dataset[8,33,34]. In 2019, a Swedish population-based cohort study of 212101 singleton pregnancies analyzed different thresholds across population, customized and Intergrowth-21 charts: the Authors concluded that no fixed thresholds reflected the risk of AO among any growth chart[35]. Liauw et al. showed that growth charts have similar performance in identifying FGR babies with higher chances of AO[36]. A nationwide population-based study of 2.4 million singleton births confirmed marked variation and no best standard to predict perinatal mortality and morbidity[37]. Birthweights (which are unknown till delivery) were used for prediction. The current study uses ultrasound EFW and substantive morbidity measures. Our data support the findings of Choi et al.[37], since neither prescriptive nor descriptive charts for fetal growth assessment improved FGR definitions performances. The inability to distinguish between normal and pathological growth before birth remains invariably unsolved by choosing different definitions and growth charts[38].

Nonetheless, antenatal detection of smallness allows for high surveillance and timely delivery, thus preventing a number of adverse events[22]. Small estimated fetal size proves to be an independent predictor of AO, as evidenced by logistic regression where EFW below the 5th

centiles was consistently associated with increased odds of AO. Despite intervention bias, the number of AO was higher in non-FGR pregnancies. This was the case regardless of definitions and references. Small fetuses are at a higher risk of morbidity and mortality[39-41]. However, our results show that birth of a normal (or large) size fetus is far more common, thus most AO affect non-antenatally suspected SGA pregnancies. There are several possible reasons why size assessment alone or in combination with other functional indices persistently fail to predict a significant number of pathological pregnancies. First, charts and definitions of 'growth restriction' use fixed cut-offs which cannot reliably capture both physiological and pathological variability in fetal development, the latter being when the fetus does not meet its growth potential[6]. The uniformly low sensitivity of FGR definitions supports the fact that fetal size is a continuous variables which cannot be easily dichotomized[3]. Our study shows that the use of any individual ultrasound parameter such as EFW or Doppler indices of maternal or fetal vessels is not appropriate because of correlation. The integration of all these parameters is advocated to overcome the limitations of using them in isolation.

Since many stillbirths and perinatal deaths are attributed to placental insufficiency[42,43], it is not surprising that UtAD was strongly associated with AO irrespective of chosen reference charts and FGR definitions[44]. Perinatal morbidity also relates to intrapartum events, in this respect fetal markers of chronic hypoxia bring limited support[45,46]. The time frame from the index scan and the adverse perinatal event is also a meaningful variable, with the most significant results being within two weeks from assessment[47]. In our study, median gestational age at scan was 36.4 weeks while median gestational age at delivery was 39.7 weeks. It has previously been shown that scans at 36-37 weeks are better in predicting the birth of a small newborn[48]. This variability, among other possible antenatal and intrapartum variables, could account for the overall disappointing performance of FGR definitions[45].

This study has several strengths and limitations. First, strength lies in the scale of a tertiary referral centre with access to a large number of pregnancies from routine clinical practice. Second, our study compares the most recognized definitions of FGR in predicting CAPO other than birthweight. By not including SGA at birth as an adverse event, we have avoided the test to become a self-fulfilling prophesy. We also acknowledge some limitations. Though we selected only the most severe AO, there is still consistent overlap between true hypoxia-related complications and iatrogenic preterm birth[49]. Having considered only the examination closest to delivery date, consensus definition decline in centiles was not evaluated, which may have underestimated its performances. However, reduced longitudinal fetal growth likely affects only a minority of pregnancies[50]. Moreover, growth velocity showed poor performances in AO prediction in a low-risk population[51]. Due to the retrospective nature of the study, results

of the ultrasound examination were available to the clinicians, intervention bias should be acknowledged. It is remarkable that maternal Dopplers retained their correlation with adverse perinatal outcome despite the results being available for management of the pregnancy. We speculate that the odds ratios for the predictors may be even higher, should the clinicians be blinded to the results. Finally, outcome data was missing for some, but this was for <10% of the pregnancies.

Conclusions

The prevalence of FGR varies depending on definitions and growth charts used. Irrespective of criteria and references used, 'FGR' has a uniformly low sensitivity for the prediction of adverse perinatal outcome. Abnormal uterine artery Doppler mean PI, abnormally low CPR and low EFW are all significantly associated with adverse perinatal outcome and these predictors are significantly correlated. Therefore, it is unsound to use individual ultrasound parameters. The integration of all these parameters into a prediction algorithm for the identification of at-risk pregnancies is advocated.

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FIGURE LEGENDS

Figure 1. Population flowchart showing pregnancies included in the study and prevalence of FGR with different definitions (ISUOG, International Society of Ultrasound in Obstetrics and Gynecology; SMFM, Society for Maternal–Fetal Medicine; Swedish definition) and growth charts (IG-21, Intergrowth-21; FMF, Fetal Medicine Foundation; Hadlock).

Figure 2. Performance of definitions and growth charts.

Table 1. Population characteristics

	All n = 17261	**Adverse perinatal outcome n = 521**	**No adverse perinatal outcome n =16740**	**p**
Maternal age (years)	33 (29.3 – 36.3)	32 (28 – 35)	33 (29 – 36)	<.001
BMI (kg/m^2)	24.6 (22 – 28.5)	25 (22.6 – 29.8)	25 (22 – 28.5)	.076
Nulliparous* (n = 11368)	5879 (52%)	182 (35%)	5697 (34%)	.71
Ethnicity* (n = 16721)				<.05
White	11232 (65.3%)	293 (59%)	10581 (65%)	
Black	2352 (13.7%)	79 (16%)	2220 (14%)	
East Asian	427 (2.5%)	17 (3%)	401 (2.5%)	
South Asian	3009 (17.5%)	105 (21%)	2854 (17.5%)	
Other	83 (1.11%)	4 (1%)	167 (1%)	
Preterm birth	612 (3.55%)	39 (7.4%)	573 (3.4%)	<.001
GA at birth (weeks)	39.7 (39 – 40.6)	39.9 (38.6 – 40.7)	39.7 (39 – 40.6)	<.001
Birthweight (gm)	3233 (2810 – 3600)	3120 (2589 – 3635)	3220 (2820 – 3600)	<.001
Birthweight centile (Hadlock)	43.9 (19.7 – 69.8)	49.1 (18.3 – 75.2)	43.7 (19.7 – 69.7)	.15
GA at scan (weeks)	36.4 (36 – 36.7)	36.1 (33.3 – 36.7)	36.3 (36 – 36.7)	<.001
Ut A PI centile	40.8 (18.8 – 67.9)	43.8 (21 – 72.8)	40.8 (18.8 – 67.8)	<.05
Umb A PI centile	48.2 (25.2 – 71)	46.8 (21.7 – 68.8)	48.25 (25.3 – 71.3)	.37
MCA PI centile	48.7 (25.8 – 72.6)	45.7 (23.3 – 70.8)	48.8 (25.8 – 72.6)	.11
CPR centile	54.4 (31.8 – 76.4)	53.8 (30.8 – 76.6)	54.5 (31.8 – 76-5)	.85

*Data are given as median (interquartile range) or n (%). Denominators vary in some characteristics shown owing to missing values. *Ethnicity and parity information was not available for the whole cohort.*

Table 2. Performance of EFW charts (first row) in detecting FGR associated with adverse outcome across different FGR definitions (second row)

	INTERGROWTH		HADLOCK		FMF		SWEDISH
	ISUOG	**SMFM**	**ISUOG**	**SMFM**	**ISUOG**	**SMFM**	**<= -2 SD**
Prevalence (%)	1.47	2.87	3.55	8.82	4.5	10.6	1.87
Sn (%)	4.4 (2.8-6.5)	6.33 (4.4-8.8)	7.68 (5.5-10.3)	11.1 (8.6-14.1)	8.1 (5.9-10.7)	13.24 (10.4-16.5)	4.99 (3.3-7.2)
Sp (%)	98.6 (98.4-98.8)	97.3 (97-97.5)	96.6 (96.3-96.8)	91.25 (90.8-91.7)	95.5 (95.2-95.8)	89.4 (88.9-89.9)	98.24 (98-98.4)
+ve LR	3.2 (2.1-4.8)	2.29 (1.6-3.2)	2.24 (1.6-3)	1.27 (.99-1.6)	1.81 (1.3-2.4)	1.25 (1-1.57)	2.84 (1.9-4.1)
-ve LR	0.97 (.95-.99)	0.96 (.94-.99)	0.96 (.93-.98)	0.97 (.94-1)	0.96 (.94-.99)	0.97 (.94-1)	0.97 (.95-.99)
PPV (%)	9.02 (6.1-13.1)	6.64 (4.8-9.1)	6.51 (4.9-8.7)	3.81 (3-4.83)	5.33 (4-7)	3.76 (3-4.7)	8.02 (5.6-11.4)
NPV (%)	97.1 (97-97.12)	97.1 (97-97.15)	97.1 (97-97.2)	97.06 (97-97.1)	97.1 (97-97.2)	97.1 (97-97.16)	97.11 (97-97.13)

ISUOG = International Society of Ultrasound in Obstetrics and Gynecology; FMF = Fetal Medicine Foundation; FGR = Fetal growth restriction; Sn = Sensitivity; Sp = Specificity; LR = Likelihood Ratio; PPV = Positive Predictive Value; NPV = Negative Predictive Value.

Table 3. Association between ultrasound indices according to IG-21, Hadlock, FMF and Swedish references and composite perinatal adverse outcomes

	Unadjusted Odds Ratio (OR)								Adjusted Odds Ratio (aOR)							
	INTERGROWTH		HADLOCK		FMF		Swedish		INTERGROWTH		HADLOCK		FMF		Swedish	
	OR (95% CI)	Sign.	OR (95% CI)	Sign.	OR (95% CI)	Sign.	OR (95% CI)	Sign.	aOR (95% CI)	Sign.	aOR (95% CI)	Sign.	aOR (95% CI)	Sign.	aOR (95% CI)	Sign.
EFW < 5th centile	6.32 (3.78 – 10.1)	**<.001**	2.1 (1.31 – 3.2)	**<.001**	1.64 (1.97 – 2.2)	**<.01**	2.9 (1.88 – 4.3)	**<.001**	5.576 (3.397 – 9.152)	**<.001**	1.810 (1.180 – 2.777)	**<.05**	1.545 (1.143 – 2.088)	**<.05**	2.508 (1.663 – 3.782)	**<.001**
CPR < 5th centile	1.74 (1.1 – 2.64)	**<.05**	1.74 (1.1 – 2.64)	**<.05**	1.74 (1.1 – 2.64)	**<.05**	1.74 (1.1 – 2.64)	**<.05**	1.186 (0.756 – 1.860)	.457	1.574 (1.038 – 2.385)	**<.05**	1.583 (1.051 – 2.383)	**<.05**	1.442 (0.947 – 2.197)	.088
UTAD > 95th centile	2.02 (1.41 – 2.8)	**<.001**	2.02 (1.41 – 2.8)	**<.001**	2.02 (1.41 – 2.8)	**<.001**	2.02 (1.41 – 2.8)	**<.001**	1.523 (1.068 – 2.171)	**<.05**	1.715 (1.217 – 2.417)	**<.05**	1.749 (1.248 – 2.449)	**<.05**	1.611 (1.138 – 2.281)	**<.05**

Multivariate logistic regression for adverse outcome prediction using multiple independent variables (aOR, adjusted Odds Ratio; CI, Confidence Interval; EFW, Estimated Fetal Weight; CPR, Cerebroplacental Ratio; UTAD, Uterine Artery Doppler)

Numerosity of EFW < 5th centile according to Intergrowth n = 125/17261 (0.7%), according to Hadlock n = 367/17261 (2.1%), according to FMF n = 997/17261(5.8%) , according to Swedish definition n = 324/17261 (1.9%) ; Numerosity of CPR < 5th centile n = 434/17261 (2.5%); numerosity of UTAD > 95th centile n = 665/17261 (3.8%)

Table 4. Correlations between explanatory variables

	SGA (IG-21)	Abnormal Ut A Doppler PI	Abnormal umbilical artery PI	Abnormal CPR	Abnormal MCA
SGA (IG-21)	1	0.258*	0.179*	0.253*	0.14*
Abnormal Ut A Doppler PI		1	0.135*	0.160*	0.11*
Abnormal umbilical artery PI			1	0.408**	0.11*
Abnormal CPR				1	0.36**
Abnormal MCA					1

*Values are Spearman's correlation coefficient, * p <0.001, ** p <0.0005*