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

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KEYWORDS: adverse outcome; Doppler; fetal growth restriction; growth chart; prenatal diagnosis; small-for-gestational age; ultrasonography

CONTRIBUTION

What are the novel findings of this work?
With uniformly low sensitivities, neither prescriptive nor descriptive fetal growth charts improve the performance of various definitions of fetal growth restriction (FGR). On multivariate logistic regression analysis, uterine artery Doppler and estimated fetal weight (EFW) < 5th percentile were the only parameters consistently associated with adverse outcome, irrespective of the definitions or growth references used.

What are the clinical implications of this work?
There is no specific definition of FGR and/or growth chart that facilitates the distinction between normal and pathological fetal growth. Use of a single ultrasound parameter, such as EFW or a maternal–fetal Doppler index, to predict adverse outcome is complicated by close correlation, so their integration into a compound prediction algorithm is advised.

ABSTRACT

Objective *Antenatal growth assessment using ultrasound aims to identify small fetuses that are at higher risk of perinatal morbidity and mortality. This study explored whether the association between suboptimal fetal growth and adverse perinatal outcome varies with different definitions of fetal growth restriction (FGR) and different weight charts/standards.*

Methods *This was a retrospective cohort study of 17 261 singleton non-anomalous pregnancies at ≥ 24 + 0 weeks' gestation that underwent routine ultrasound at a tertiary referral hospital. Estimated fetal weight (EFW) and Doppler indices were converted into percentiles using a reference standard (INTERGROWTH-21st (IG-21)) and various reference charts (Hadlock, Fetal Medicine Foundation (FMF) and Swedish). Test characteristics were assessed using the consensus definition, Society for Maternal–Fetal Medicine (SMFM) definition and Swedish criteria for FGR. Adverse perinatal outcome was defined as perinatal death, admission to the neonatal intensive care unit at term, 5-min Apgar score < 7 and therapeutic cooling for neonatal encephalopathy. The association between FGR according to each definition and adverse perinatal outcome was compared. Multivariate logistic regression analysis was used to test the strength of association between ultrasound parameters and adverse perinatal outcome. Ultrasound parameters were also tested for correlation.*

Results *IG-21, Hadlock and FMF fetal size references classified as growth-restricted 1.5%, 3.6% and 4.6% of fetuses, respectively, using the consensus definition and 2.9%, 8.8% and 10.6% of fetuses, respectively, using the SMFM definition. The sensitivity of the definition/chart combinations for adverse perinatal outcome varied from 4.4% (consensus definition with IG-21 charts) to 13.2% (SMFM definition with FMF charts). Specificity varied from 89.4% (SMFM definition with FMF charts) to 98.6% (consensus definition with IG-21 charts). The consensus definition and Swedish criteria showed the highest specificity, positive predictive value and positive likelihood ratio in detecting adverse outcome, irrespective of the reference chart/standard used. Conversely, the*

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SMFM definition had the highest sensitivity across all investigated growth charts. Low EFW, abnormal mean uterine artery pulsatility index (UtA-PI) and abnormal cerebroplacental ratio were significantly associated with adverse perinatal outcome and there was a positive correlation between the covariates. Multivariate logistic regression showed that UtA-PI > 95th percentile and EFW < 5th percentile were the only parameters consistently associated with adverse outcome, irrespective of the definitions or fetal growth chart/standard used.

Conclusions *The apparent prevalence of FGR varies according to the definition and fetal size reference chart/standard used. Irrespective of the method of classification, the sensitivity for the identification of adverse perinatal outcome remains low. EFW, UtA-PI and fetal Doppler parameters are significant predictors of adverse perinatal outcome. As these indices are correlated with one other, a prediction algorithm is advocated to overcome the limitations of using these parameters in isolation.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Fetal growth restriction (FGR) is known to be associated with a significant burden of perinatal mortality and morbidity[1]. Over the years, significant effort has been put into the prenatal detection of fetal smallness, with significant variation in the size thresholds used and the detection rates achieved[2,3]. Antenatal assessment of fetal size using ultrasound has been the primary modality to identify growth abnormalities. Estimated fetal weight (EFW) below the 10th percentile is referred to as FGR or small for gestational age (SGA) according to the American College of Obstetricians and Gynecologists[4], a definition adopted by the Society for Maternal–Fetal Medicine (SMFM)[5]. Although smallness alone is not necessarily sufficient to warrant a diagnosis of FGR according to the consensus definition[6], it is an integral component for qualifying the diagnosis. The performance of various definitions of FGR in predicting low birth weight has been compared[7]. However, smallness is not a disease in itself; it can represent 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, EFW percentiles greatly vary according to the chart used[8,9].

The Pregnancy Outcome Prediction study[10] reported that smallness alone has limited sensitivity for neonatal morbidity. The threshold used could explain this. It may also be related to the use of a specific size standard to assess the extent of deviation from the expected size. Birth weight is, by definition, unknown until the baby is born. Therefore, it is not appropriate to use it as a predictor for morbidity or as a means to decide on intervention. Birth weight is influenced by gestational age at delivery and preterm births pose an unsolvable bias in creating optimal references[11]. Therefore, EFW rather than birth weight is a more appropriate measure to guide intervention.

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

METHODS

Study design and cohort

This was a single-center retrospective cohort study of women who attended for antenatal ultrasound examinations at St George's University Hospital, London, UK, a tertiary referral hospital, between April 2016 and March 2022. Since all pregnant women at St George's University Hospital are offered a routine ultrasound examination at between 36 and 37 weeks' gestation, the population comprises both high- and low-risk pregnancies. When EFW is noted to be < 10th percentile, serial growth scans are arranged. Induction of labor is offered from 37 weeks for EFW < 5th percentile and from 39 weeks for EFW < 10th percentile. Ultrasound 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 Group, Mansfield, UK). Confirmation was obtained from the ethics committee that formal ethical approval was not required for this retrospective study of routinely collected data.

Inclusion criteria were a singleton pregnancy at ≥ 24 + 0 weeks' gestation, with no evidence of fetal structural or chromosomal abnormality and with known birth outcome. Gestational age was assigned at a dating scan in the first trimester using crown–rump length measurement according to the UK National Institute for Health and Care Excellence guidelines[12]. Multiple pregnancies, pregnancies with known fetal abnormality and those 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 include maternal characteristics (age, body mass index, parity and ethnicity), ultrasound parameters (fetal biometry and uterine artery (UtA), umbilical artery (UA) and fetal middle cerebral artery (MCA) Doppler indices) and birth outcomes (gestational age at delivery, birth weight, gender, Apgar score, admission to the neonatal intensive care unit (NICU) and therapeutic cooling for neonatal encephalopathy).

Ultrasound measurements were obtained according to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG)[13]. EFW was calculated using the Hadlock formula[14]. Percentiles for EFW and abdominal circumference were calculated according to both a reference standard (INTERGROWTH-21st (IG-21)[15,16]) and reference charts (Hadlock[17] and Fetal

Medicine Foundation (FMF)[18]). For the Swedish definition of SGA[19], EFW was calculated using the formula developed by Persson and Weldner[20]. Deviation of the EFW by more than 22% from the expected weight was used to identify SGA fetuses, as described previously[21,22], but this criterion mainly identifies severe SGA, since the lowest 10th percentile is equivalent to a weight deviation of less than 16.5%.

UtA pulsatility index (PI) on the left and right sides were averaged and the mean was considered abnormal if it exceeded the 95th percentile according to the reference ranges of Gómez *et al.*[23]. IG-21[24] and FMF[25] reference ranges were used to assess UA-PI, MCA-PI and the cerebroplacental ratio (CPR). Abnormality was defined as UA-PI $>95^{th}$ percentile, MCA-PI $<5^{th}$ percentile and CPR $<5^{th}$ percentile[25]. Other Doppler references charts were compared for late FGR using the consensus definition[26,27].

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

Statistical analysis

Sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios were compared for the consensus[6], SMFM[5] and Swedish[21] definitions. Multivariate logistic regression analysis was applied for four potential predictors of adverse outcome: smallness (EFW $<5^{th}$ percentile), abnormal UtA-PI, abnormal UA-PI and abnormal CPR. Since UA-PI and CPR are highly likely to be correlated, introducing multicollinearity, we used Pearson correlation to test this hypothesis and then performed two logistic regression analyses with predictors that included either UA-PI or CPR. Since the 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 version 28.0 (IBM Corp., Armonk, NY, USA). Data are reported as median (interquartile range) for continuous variables and *n* (%) for categorical variables.

RESULTS

Among 19 084 pregnancies seen over the 6-year period, 17 261 (90.4%) met the inclusion criteria (Figure 1), of which 521 (3.0%) experienced at least one of the pre-specified adverse outcomes. The frequency of individual adverse outcomes is shown in Table S1. The choice to include NICU admission of only term infants within the composite outcome makes our cohort representative of the most severe adverse outcome solely related to FGR in term pregnancies.

Population characteristics are summarized in Table 1. The cohort was represented mainly by nulliparous women (51.7%) and those with white ethnicity (65.0%). On univariate analysis, significant differences were seen between pregnancies with and those without adverse outcome in maternal age, ethnicity, rate of preterm birth, gestational age at scan and at birth, birth weight and maternal Doppler measurements.

The prevalence of FGR varied in our cohort according to the definition and growth chart used (Figure 1, Table 2). The prevalence of FGR identified by the consensus definition was 1.5%, 3.6% and 4.6% according to the IG-21, Hadlock and FMF growth

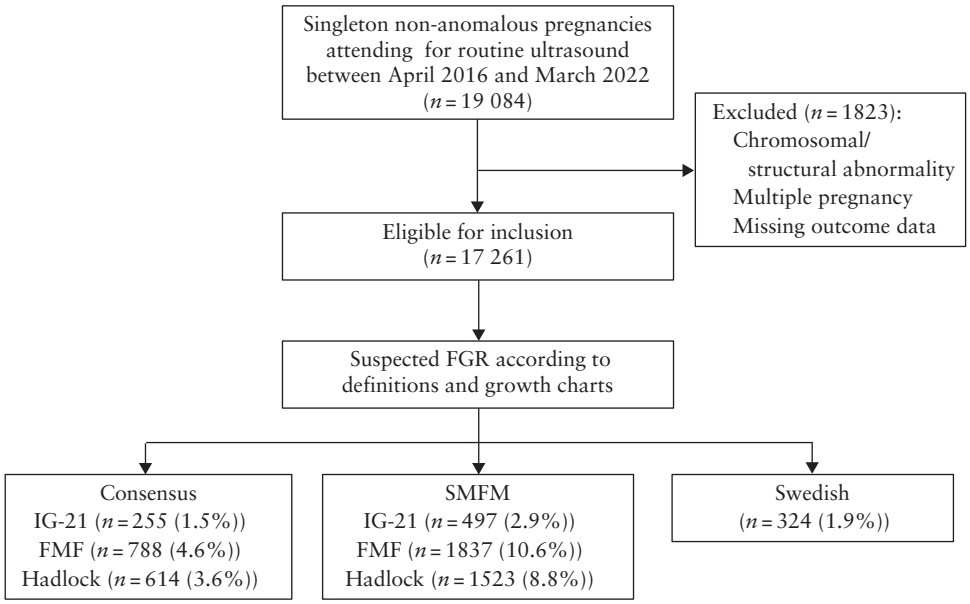

Figure 1 Flowchart summarizing inclusion of pregnancies in study and prevalence of fetal growth restriction (FGR) according to different definitions (Delphi consensus; Society for Maternal–Fetal Medicine (SMFM); Swedish definition) and growth charts (INTERGROWTH-21st (IG-21); Fetal Medicine Foundation (FMF); Hadlock).

charts, respectively. Separate analyses for early *vs* late FGR identified by the consensus definition are available in Table S2. Other Doppler reference charts were considered and showed comparable results for late FGR (Table S3). SMFM criteria categorized 2.9%, 8.8% and 10.6% of fetuses in the study population as growth restricted. The Swedish definition, namely a deviation by more than −22% from EFW references, identified 1.9% of fetuses as abnormally small. Overall, the descriptive growth charts (Hadlock, FMF and Swedish) classified more fetuses as growth restricted than did the prescriptive IG-21 antenatal standards.

The performance of EFW charts in detecting FGR associated with adverse outcome is shown in Table 2. Median sensitivity was 7.7%, ranging from 4.4% (consensus definition applied to IG-21 charts) to 13.2% (SMFM definition applied to FMF charts). Median specificity was 96.6%, ranging from 89.4% (SMFM definition applied to FMF charts) to 98.6% (consensus definition applied to IG-21 charts). Irrespective of the growth chart used, the consensus and Swedish criteria showed the highest specificity, positive predictive value and positive likelihood ratio in detecting adverse outcome among SGA fetuses. Conversely, the SMFM definition had the highest sensitivity. Negative predictive values and negative likelihood ratios were similar across all definitions of SGA.

Several ultrasound indices (EFW < 5th percentile, UA-PI > 95th percentile, CPR < 5th percentile and UtA-PI > 95th

Table 1 Demographic and clinical characteristics of study population, according to occurrence of adverse perinatal outcome

Characteristic	*All* (n = *17 261*)	*Adverse perinatal outcome* (n = *521*)	*No adverse perinatal outcome* (n = *16 740*)	P
Maternal age (years)	33.0 (29.3–36.3)	32.0 (28.0–35.0)	33.0 (29.0–36.0)	< 0.001
BMI (kg/m^2)	24.6 (22.0–28.5)	25.0 (22.6–29.8)	25.2 (22.0–28.5)	0.08
Nulliparous	5879/11 368 (51.7)	182 (34.9)	5697/10 847 (52.5)	0.71
Ethnicity				0.04
White	10 874/16 721 (65.0)	293/498 (58.8)	10 581/16 223 (65.2)	
Black	2299/16 721 (13.7)	79/498 (15.9)	2220/16 223 (13.7)	
East Asian	418/16 721 (2.5)	17/498 (3.4)	401/16 223 (2.5)	
South Asian	2959/16 721 (17.7)	105/498 (21.1)	2854/16 223 (17.6)	
Other	171/16 721 (1.0)	4/498 (0.8)	167/16 223 (1.0)	
Preterm birth	612 (3.5)	39 (7.5)	573 (3.4)	< 0.001
GA at birth (weeks)	39.7 (39.0–40.6)	39.9 (38.6–40.7)	39.7 (39.0–40.6)	< 0.001
Birth weight (g)	3233 (2810–3600)	3120 (2589–3635)	3220 (2820–3600)	< 0.001
Birth-weight percentile (Hadlock)	43.9 (19.7–69.8)	49.1 (18.3–75.2)	43.7 (19.7–69.7)	0.15
GA at scan (weeks)	36.4 (36.0–36.7)	36.1 (33.3–36.7)	36.3 (36.0–36.7)	< 0.001
UtA-PI percentile	40.8 (18.8–67.9)	43.8 (21.0–72.8)	40.8 (18.8–67.8)	0.03
UA-PI percentile	48.2 (25.2–71.0)	46.8 (21.7–68.8)	48.3 (25.3–71.3)	0.37
MCA-PI percentile	48.7 (25.8–72.6)	45.7 (23.3–70.8)	48.8 (25.8–72.6)	0.11
CPR percentile	54.4 (31.8–76.4)	53.8 (30.8–76.6)	54.5 (31.8–76.5)	0.85

Data are given as median (interquartile range), *n/N* (%) or *n* (%). Body mass index (BMI), ethnicity and parity information was not available for the whole cohort. CPR, cerebroplacental ratio; GA, gestational age; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

Table 2 Performance of estimated fetal weight charts (first row) in detecting fetal growth restriction (FGR) associated with adverse outcome according to different FGR definitions (second row)

	IG-21		*Hadlock*		*FMF*		
Parameter	*Consensus*	*SMFM*	*Consensus*	*SMFM*	*Consensus*	*SMFM*	*Swedish*
Prevalence (%)	1.5	2.9	3.6	8.8	4.6	10.6	1.9
Sensitivity (%)	4.4 (2.8–6.5)	6.3 (4.4–8.8)	7.7 (5.5–10.3)	11.1 (8.6–14.1)	8.1 (5.9–10.7)	13.2 (10.4–16.5)	5.0 (3.3–7.2)
Specificity (%)	98.6 (98.4–98.8)	97.3 (97.0–97.5)	96.6 (96.3–96.8)	91.3 (90.8–91.7)	95.5 (95.2–95.8)	89.4 (88.9–89.9)	98.2 (98.0–98.4)
LR+	3.2 (2.1–4.8)	2.3 (1.6–3.2)	2.2 (1.6–3.0)	1.3 (1.0–1.6)	1.8 (1.3–2.4)	1.3 (1.0–1.6)	2.8 (1.9–4.1)
LR−	0.97 (0.95–0.99)	0.96 (0.94–0.99)	0.96 (0.93–0.98)	0.97 (0.94–1.00)	0.96 (0.94–0.99)	0.97 (0.94–1.00)	0.97 (0.95–0.99)
PPV (%)	9.0 (6.1–13.1)	6.6 (4.8–9.1)	6.5 (4.9–8.7)	3.8 (3.0–4.8)	5.3 (4.0–7.0)	3.8 (3.0–4.7)	8.0 (5.6–11.4)
NPV (%)	97.1 (97.0–97.1)	97.1 (97.0–97.2)	97.1 (97.0–97.2)	97.1 (97.0–97.1)	97.1 (97.0–97.2)	97.1 (97.0–97.2)	97.1 (97.0–97.1)

Values in parentheses are 95% CI. FMF, Fetal Medicine Foundation; IG-21, INTERGROWTH-21st; LR+, positive likelihood ratio; LR−, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; SMFM, Society for Maternal–Fetal Medicine.

percentile) were examined for their association with adverse perinatal outcome (Tables 3 and 4). In order to identify multicollinearity between abnormal UA-PI, MCA-PI and CPR, Spearman's test was performed (Table 5). Because of moderate correlation ($\rho = 0.41$, $P < 0.0005$) between abnormal UA-PI and abnormal CPR, UA-PI was excluded from multivariate logistic regression analysis. Regarding EFW, different percentile charts were considered (Table 3, Figure 2). Overall, multivariate logistic regression analysis identified abnormal UtA Doppler and EFW < 5th percentile as significant independent predictors of adverse outcome, irrespective of the reference chart used. UtA Doppler contributed independently to outcome prediction among all charts investigated, with $P < 0.05$ in all cases and an adjusted odds ratio (aOR) ranging from 1.523 to 1.749 (Table 4). Even greater significance was found for EFW < 5th percentile across the four growth charts analyzed (aOR, 1.545–5.576). Conversely, differences in fetal Doppler data did not consistently reach statistical significance. Only when considering the Hadlock and FMF charts did CPR reach significance, with

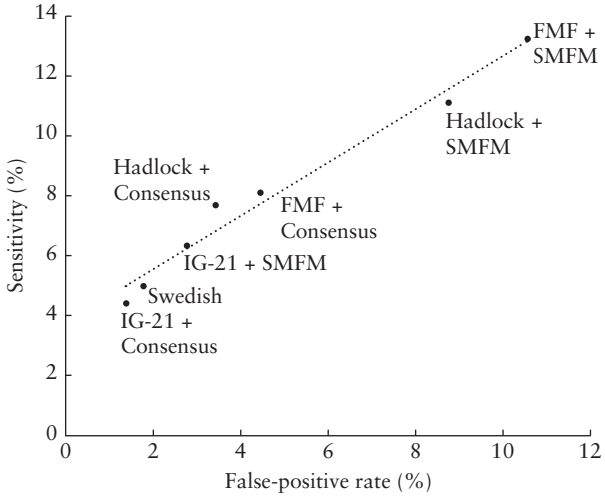

Figure 2 Performance of different definitions of fetal growth restriction (Delphi consensus; Society for Maternal–Fetal Medicine (SMFM); Swedish definition) and growth charts (INTERGROWTH-21st (IG-21); Fetal Medicine Foundation (FMF); Hadlock) in predicting adverse perinatal outcome.

Table 3 Multivariate logistic regression analysis of association between estimated fetal weight < 5th percentile according to INTERGROWTH-21st (IG-21), Hadlock, Fetal Medicine Foundation (FMF) and Swedish references and composite adverse perinatal outcome in 17 261 pregnancies

Reference	n *(%)*	*OR (95% CI)*	P	*aOR (95% CI)*	P
IG-21	125 (0.7)	6.3 (3.8–10.1)	< 0.001	5.576 (3.397–9.152)	< 0.001
Hadlock	367 (2.1)	2.1 (1.3–3.2)	< 0.001	1.810 (1.180–2.777)	0.007
FMF	997 (5.8)	2.1 (2.0–2.2)	< 0.01	1.545 (1.143–2.088)	0.005
Swedish	324 (1.9)	2.9 (1.9–4.3)	< 0.001	2.508 (1.663–3.782)	< 0.001

aOR, adjusted odds ratio; OR, odds ratio.

Table 4 Multivariate logistic regression analysis of association between Doppler indices and composite adverse perinatal outcome in 17 261 pregnancies

				IG-21		*Hadlock*		*FMF*		*Swedish*	
Index	n *(%)*	*OR (95% CI)*	P	*aOR (95% CI)*	P	*aOR (95% CI)*	P	*aOR (95% CI)*	P	*aOR (95% CI)*	P
CPR < p5	434 (2.5)	1.7 (1.1–2.6)	0.0125	1.186 (0.756–1.860)	0.457	1.574 (1.038–2.385)	0.033	1.583 (1.051–2.383)	0.028	1.442 (0.947–2.197)	0.088
UtA-PI > p95	665 (3.9)	2.0 (1.4–2.8)	< 0.001	1.523 (1.068–2.171)	0.02	1.715 (1.217–2.417)	0.002	1.749 (1.248–2.449)	0.001	1.611 (1.138–2.281)	0.007

aOR, adjusted odds ratio; CPR, cerebroplacental ratio; FMF, Fetal Medicine Foundation; IG-21, INTERGROWTH-21st; OR, odds ratio; p5, 5th percentile; p95, 95th percentile; UtA-PI, uterine artery pulsatility index.

Table 5 Correlation between explanatory variables

Variable	*EFW < p5**	*UtA-PI > p95*	*UA-PI > p95*	*CPR < p5*	*MCA-PI < p5*
EFW < p5*	1	0.26†	0.18†	0.25†	0.14†
UtA-PI > p95	—	1	0.14†	0.16†	0.11†
UA-PI > p95	—	—	1	0.41‡	0.11†
CPR < p5	—	—	—	1	0.36‡
MCA-PI < p5	—	—	—	—	1

Values are Spearman's correlation coefficient. *According to INTERGROWTH-21st reference. †$P < 0.001$. ‡$P < 0.0005$. CPR, cerebroplacental ratio; EFW, estimated fetal weight; MCA, middle cerebral artery; p5, 5th percentile; p95, 95th percentile; PI, pulsatility index; UA, umbilical artery; UtA, uterine artery.

aORs of 1.574 (95% CI, 1.038–2.385; $P = 0.033$) and 1.583 (95% CI, 1.051–2.383; $P = 0.028$), respectively. Using the IG-21 and Swedish charts, CPR had an aOR of 1.186 (95% CI, 0.756–1.860; $P = 0.457$) and 1.442 (95% CI, 0.947–2.197; $P = 0.088$), respectively. The significant correlation between parameters (Table 5) explains why they were highly significant on univariate analysis, but the significance became inconsistent on multivariate analysis.

DISCUSSION

Identifying FGR pregnancies is a key element of antenatal programs aimed at reducing perinatal morbidity and mortality. The outcome 'low birth weight' 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 being associated with adverse perinatal outcome[30,31]. In our cohort, the less stringent SMFM criteria indicated a doubling in the numbers of putative FGR fetuses compared with the consensus definition. Nevertheless, the sensitivity remained low regardless of the chosen definition. These findings align with those of Roeckner *et al.*[7], who reported sensitivities of 10.1% (consensus definition) and 15.1% (SMFM definition) in predicting composite adverse outcome. In their study of 1054 pregnancies, the prevalence of adverse outcome was 13.2%, compared with 3.0% in this study. The difference is most likely owing to the chosen definition of 'adverse perinatal outcome'. Roeckner *et al.* included all NICU admissions, whereas the present study included only term NICU admissions. In 2022, Schreiber *et al.*[32] compared the performance of the SMFM and consensus criteria for predicting composite severe neonatal morbidity, with similarly disappointing sensitivity for both (8.4% and 4.9%, respectively). Composite severe neonatal morbidity was seen in 17.8% of the 18 406 births designated as non-FGR and 31.8% of the 1030 births classified using either set of criteria as 'late FGR'. This high prevalence was driven mainly by hypoglycemia.

We also showed that the sensitivity of FGR definitions is low irrespective of the growth chart used. The subtle differences between prescriptive and descriptive charts are known to give rise to variable detection rates of 'FGR' even within the same dataset[8,33,34]. In 2019, a Swedish population-based cohort study of 212 101 singleton pregnancies analyzed different thresholds across population, customized and IG-21 charts[35]. The authors concluded that no fixed thresholds reflected the risk of adverse outcome across the different growth charts[35]. Liauw *et al.*[36] showed that three growth charts (IG-21, World Health Organization and Hadlock) have a similar performance in identifying FGR pregnancies with higher chances of adverse outcome. A nationwide population-based study of 2.4 million singleton births by Choi *et al.*[37] confirmed marked variation between growth standards and identified no superior standard for predicting perinatal mortality and morbidity. Birth-weight and EFW charts had similarly poor performance in predicting adverse outcome. The current study uses ultrasound EFW and measures of substantive morbidity. Our data support the findings of Choi *et al.*[37], since neither prescriptive nor descriptive charts for fetal growth assessment improved the performance of FGR definitions. The question of how to distinguish between normal and pathological growth before birth remains unsolved by choosing different definitions and growth charts[38].

Nonetheless, antenatal detection of smallness allows for enhanced surveillance and timely delivery, thus reducing the number of adverse events[22]. Small estimated fetal size is an independent predictor of adverse outcome, as evidenced by our multivariate logistic regression analysis, which found that EFW $< 5^{th}$ percentile was associated consistently with increased odds of adverse outcome, despite intervention bias. This was the case regardless of the definitions and references used. Small fetuses are at a higher risk of morbidity and mortality[9,39,40]. However, our results show that the birth of a normal-sized (or large) fetus is far more common, thus most instances of adverse outcome affect pregnancies without an antenatal suspicion of SGA. There are several possible reasons why size assessment alone or in combination with other functional indices fails consistently to predict a significant number of pathological pregnancies. First, charts and definitions of FGR use fixed cut-offs that 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 variable that cannot easily be 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 close correlation. Integration of these parameters is advocated to overcome the limitations of using them in isolation.

Since many stillbirths and perinatal deaths are attributed to placental insufficiency[41,42], it is unsurprising that UtA-PI was associated strongly with adverse outcome, irrespective of the reference chart and FGR definition employed[43]. Perinatal morbidity also relates to intrapartum events, and in this respect fetal markers of chronic hypoxia bring limited support[44,45]. The interval between the index scan and the adverse perinatal event is also a meaningful variable, with the best predictive performance for events within 2 weeks after assessment[46]. In our study, the median gestational age at ultrasound was 36.4 weeks, while that at delivery was 39.7 weeks. It has been shown previously that scans at 36–37 weeks are better at predicting the birth of a small newborn[47]. This variability, among other possible antenatal and intrapartum variables, could account for the overall disappointing performance of FGR definitions[44].

This study has several strengths. First, it was conducted in a large tertiary referral center with access to data from

a large number of pregnancies obtained in routine clinical practice. Second, our study compares the most widely recognized definitions of FGR in predicting adverse perinatal outcomes excluding birth weight. By not including SGA at birth as an adverse event, we avoided the test becoming a self-fulfilling prophecy. We also acknowledge some limitations. Though we selected only the most severe adverse outcomes, there is still significant overlap between true hypoxia-related complications and iatrogenic preterm birth[48]. Having considered only the examination closest to the delivery date, it was not possible to evaluate a decline in EFW percentile, which may have led to underestimation of the performance of the consensus definition. However, reduced longitudinal fetal growth is likely to affect only a minority of pregnancies[49]. Moreover, it has been shown previously that growth velocity shows poor performance in predicting adverse outcome in a low-risk population[50]. Owing to the retrospective nature of the study, the results of the ultrasound examinations were available to clinicians, so intervention bias should be acknowledged. It is remarkable that maternal Doppler parameters retained their correlation with adverse perinatal outcome, despite the results being available for pregnancy management. We speculate that the odds ratios for the predictors would have been even higher had the clinicians been blinded to the ultrasound findings. Finally, outcome data were missing in some cases, but this was for < 10% of the study population.

In conclusion, the apparent prevalence of FGR varies depending on the definition and growth chart used. Irrespective of the criteria and references used, 'FGR' has a uniformly low sensitivity for the prediction of adverse perinatal outcome. Elevated UtA-PI and low EFW are all associated significantly with adverse perinatal outcome, and these predictors are significantly correlated. Therefore, it is unsound to use individual ultrasound parameters as predictors, and their integration into a prediction algorithm for the identification of at-risk pregnancies is advocated.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Table S1 Prevalence of individual adverse outcomes included in composite measure in preterm and term pregnancies

Table S2 Performance of estimated fetal weight charts (first row) in detecting fetal growth restriction (FGR) associated with adverse outcome according to consensus definition (second row) in early (< 32 weeks) *vs* late (≥ 32 weeks) gestation

Table S3 Performance of cerebroplacental ratio Doppler references of Wolf *et al.*[26] and Baschat *et al.*[27] in detecting late fetal growth restriction (FGR) according to consensus definition (second row) across different growth charts (first row)

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Predicción prenatal de resultados adversos utilizando diferentes tablas y definiciones de restricción del crecimiento fetal

RESUMEN

Objetivo. El objeto de la evaluación prenatal del crecimiento mediante ecografía es identificar los fetos pequeños que presentan un mayor riesgo de morbilidad y mortalidad perinatal. Este estudio exploró si la asociación entre el crecimiento fetal subóptimo y el resultado perinatal adverso varía con diferentes definiciones de restricción del crecimiento fetal (RCF) y diferentes tablas/estándares de peso.

Métodos. Se trató de un estudio de cohortes retrospectivo de 17 261 embarazos de feto único no anómalos en ≥24+0 semanas de gestación que se sometieron a ecografía rutinaria en un hospital terciario de referencia. El peso fetal estimado (PFE) y los índices Doppler se convirtieron en percentiles utilizando un estándar de referencia (INTERGROWTH-21st (IG-21)) y varias tablas de referencia (Hadlock, Fetal Medicine Foundation (FMF) y Swedish (Suecia)). Las características de la prueba se evaluaron utilizando la definición de consenso, la definición de la Sociedad de Medicina Maternofetal (SMFM) y los criterios suecos de RCF. El resultado perinatal adverso se definió como muerte perinatal, ingreso en la unidad de cuidados intensivos neonatales a término, puntuación Apgar a los 5 minutos <7 y enfriamiento terapéutico por encefalopatía neonatal. Se comparó la asociación entre la RCF, según cada definición, y los resultados perinatales adversos. Se utilizó un análisis de regresión logística multivariante para probar la robustez de la asociación entre los parámetros ecográficos y el resultado perinatal adverso. También se comprobó la correlación de los parámetros ecográficos.

Resultados. Las referencias de tamaño fetal IG-21, Hadlock y FMF se clasificaron como con restricción del crecimiento al 1,5%, 3,6% y 4,6% de los fetos, respectivamente, utilizando la definición de consenso y al 2,9%, 8,8% y 10,6% de los fetos, respectivamente, utilizando la definición de la SMFM. La sensibilidad de las combinaciones de definición y gráficas para el resultado perinatal adverso varió del 4,4% (definición de consenso con gráficas IG-21) al 13,2% (definición de la SMFM con gráficas de la FMF). La especificidad varió del 89,4% (definición de la SMFM con tablas de la FMF) al 98,6% (definición de consenso con tablas IG-21). La definición consensuada y los criterios suecos mostraron los valores más elevados de especificidad, valor predictivo positivo y cociente de verosimilitud positivo en la detección de resultados adversos, independientemente de la tabla/estándar de referencia utilizado. Por el contrario, la definición de la SMFM tuvo la mayor sensibilidad en todas las gráficas de crecimiento investigadas. Un bajo PFE, un índice medio de pulsatilidad de la arteria uterina (UtA-PI, por sus siglas en inglés) anómalo y una relación cerebroplacentaria anómala se asociaron significativamente con un resultado perinatal adverso y se observó una correlación positiva entre las covariables. La regresión logística multivariante mostró que un UtA-PI >95° percentil y un PFE <5° percentil eran los únicos parámetros asociados de forma consistente con un resultado adverso, independientemente de las definiciones o de la tabla/estándar de crecimiento fetal utilizados.

Conclusiones. La prevalencia aparente de la RCF varía según la definición y la tabla/estándar de referencia de tamaño fetal utilizados. Independientemente del método de clasificación, la sensibilidad para la identificación de resultados perinatales adversos sigue siendo baja. Los parámetros PFE, UtA-PI y Doppler fetal son predictores significativos de resultados perinatales adversos. Como estos índices están correlacionados entre sí, se aboga por un algoritmo de predicción para superar las limitaciones de utilizar estos parámetros de forma aislada.

产前使用不同胎儿体重参考图表和胎儿生长受限定义预测不良结局

摘要

目的 超声产前生长评估旨在识别围产期发病和死亡风险较高的小胎儿。本研究探讨了胎儿发育不理想与围产期不良结局之间的关系是否会因不同的胎儿生长受限（FGR）定义 和不同的体重参考图表/标准而存在差异。

方法 这是一项回顾性队列研究，对象是在一家三级转诊医院接受常规超声检查的 17261 例≥24+0周的单胎非异常妊娠。估计胎儿体重（EFW）和多普勒指数通过参考标准（INTERGROWTH-21st （IG-21））和各种参考图表（Hadlock参考图、胎儿医学基金会（FMF）参考图和瑞典参考图）转换成百分位数。检测特征采用共识定义、母胎医学会（SMFM）定义和瑞典 FGR 标准进行评估。围产期不良结局被定义为围产期死亡、足月入住新生儿重症监护室、
5 分钟阿氏评分＜7分和新生儿脑病低体温治疗。比较了每种定义下的FGR与围产期不良结局之间的关系。使用多变量逻辑回归分析检验超声参数
与围产期不良结局之间的相关性。同时还检测了超声参数的相关性。

结果 IG-21、Hadlock 及 FMF 胎儿大小参考值在共识定义中分别有 1.5%、3.6% 及 4.6%的胎儿被归类为生长受限，而在 SMFM 定义中分别有 2.9%、8.8% 及 10.6%的胎儿被归类为生长受限。不同定义/图表组合对围产期不良结局的敏感性从 4.4%（共识定义与IG-21图表组合）到13.2%（SMFM定义与FMF图表组合）不等。特异性从89.4%（SMFM定义与FMF图表组合）到98.6%（共识定义与IG-21图表组合）不等。无论使用哪种参考图表/标准，共识定义和瑞典标准的组合
在检测不良结局方面都显示出最高的特异性、阳性预测值和阳性似然比。相反，在研究所用的所有生长图表中，SMFM 定义的敏感性最高。低EFW、平均子宫动脉搏动指数（UtA-PI）异常和脑胎盘比异常
与围产期不良结局有显著相关性，并且这些协变量之间存在正相关性。多变量逻辑回归分析显示，无论使用何种定义或胎儿生长图表/标准，UtA-PI>第95百分位数和EFW<第5百分位数是唯二与不良结局一致相关的参数。

结论 FGR的报告患病率因所使用的定义和胎儿大小参考图表/标准而异。无论采用哪种分类方法，识别围产期不良结局的敏感度都很低。EFW、UtA-PI 和胎儿多普勒参数是围产期不良结局的重要预测指标。由于这些指标相互关联，
因此提倡使用预测算法来克服单独使用这些参数的局限性。