The ISUOG definition of FGR has been proposed by a Delphi procedure and includes either EFW or AC <3rd percentile or EFW or AC <10th percentile combined with abnormal Doppler findings or a decrease in growth centiles, depending on gestational age at FGR diagnosis. Abnormal Doppler criteria was either abnormal uterine artery pulsatility index (PI) a value >95th percentile, and/or abnormal umbilical artery PI as a value >95th percentile in early onset FGR and abnormal umbilical artery PI as a value >95th percentile and/or abnormal cerebroplacental ratio as a value <5th percentile in late onset FGR.

The primary outcome was to assess the accuracy of the ISUOG definition for predicting composite adverse neonatal outcome (ANO) including one or more of: neonatal intensive care unit (NICU) admission, 5-min Apgar score < 7, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis, periventricular leukomalacia, neonatal anemia, pulmonary hypertension, seizures and death.

Statistical methods:

Sample size was calculated using PASS 11 program, setting power at 80% and x-error at 0.05. Result from previous study Rizzo et al [11] showed that the expected incidence of adverse perinatal outcomes =32.5%, area under ROC curve for consensus for prediction of adverse outcomes =0.74, so sample size needed is at least 55 women that had pregnancies with FGR (EFW <10th percentile).

Data were collected, tabulated and subjected to the proper statistical analysis using SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA).

Categorical variables were presented as number and percentage and inter-group differences were compared using the Pearson chi-squared test or Fisher's exact test as appropriate. Ordinal data were compared using the chi-squared test for trend. Continuous numerical variables were presented as mean and SD. P-values <0.05 were considered statistically significant.

Multivariable binary logistic regression analysis was used to examine the relation between EFW and composite ANO as adjusted for possible confounding factors.

Receiver-operating characteristic (ROC) curve analysis was used to examine the predictive value of different ultrasound parameters in predicting composite ANO.

Results:

A total of 55 singleton pregnancies complicated by fetal growth restriction identified according to our current definition (AC or EFW <10th centile) were enrolled. Of the cohort, only 40 cases (72.7%) fulfilled the recent ISUOG criteria; therefore, the cohort was divided into two groups: FGR and non FGR group.

There was no significant difference between both groups in the baseline demographic and clinical criteria, while; birth weight differed significantly between both groups.

There was a significant difference between both groups regarding all biometric measurements and the umbilical artery pulsatility index as shown in table 2

As noted in table 3, composite ANO occurred in 21 (38.2%) of the 55 included pregnancies (all were in FGR group according ISUOG definition). The new ISUOG definition of FGR significantly succeeded in predicting composite ANO (P<0.0001) including principally RDS (P=0.001) and NICU admission (P<0.001).

Figure 1 shows that EFW had poor predictive value with an area under the ROC curve (AUC) of 0.689 (95% CI: 0.550 to 0.807, p-value: 0.0017). The best cut-off criterion is <3rd centile which had a sensitivity of 85.7% and specificity of 52.9%.

AC had good predictive value with an area under the ROC curve (AUC) of 0.807 (95% CI: 0.676 to 0.901, p-value: <0.0001). The best cut-off criterion is <3rd centile which had a sensitivity of 66.6% and specificity of 90.9% as shown in figure 2.

UAPI had fair predictive value with an area under the ROC curve (AUC) of 0.747 (95% CI: 0.612 to 0.855, p-value: 0.0014). The best cut-off criterion is >95th centile which had a sensitivity of 71.4% and specificity of 79.4%. **(figure 3).**

Discussion:

Defining FGR by the presence of aberrations in biometric measures of fetal weight and/or abdominal circumference <10th centile usually misdiagnoses healthy but constitutionally small fetuses as FGR. Thus, provoking unnecessary parental anxiety and precludes the allocation of resources to caring for the fetuses that are actually at risk for adverse outcomes [12].

The current study showed that the recent ISUOG criteria identified all pregnancies that were complicated by composite adverse neonatal outcome and SGA neonates when compared to the traditional definition (p<0.0001 and p=0.01) respectively.

According to Roeckner et al., [13] and Schreiber et al.,[14] the traditional definition (using biometric measurements only) had higher detection rates of SGA neonates. In their studies, both the definition based on biometric and Doppler parameters and that used only the biometric measurements performed poorly in predicting adverse neonatal outcomes.

Molina et al., [12] reported that the definition encompassing biometric and Doppler parameters identified more pregnancies that were significantly at risk for composite ANO when compared to the traditional definition. However; the definition encompassing biometric and Doppler parameters identified fewer SGA neonates than did the traditional definition.

The admission to the NICU mainly due to RDS is one of the most significant contributors to estimating FGR related adverse neonatal outcomes. The current study showed that ISUOG definition could accurately detect all fetal growth restricted cases that developed RDS or needed NICU admission. On the contrary, Roeckner et al.,[13] found that neither the traditional definition nor the new definition was able to predict RDS, while the new definition was associated with increased odds of NICU admission (OR, 2.3 (95% CI, 1.19–4.55).

Of the individual components of the ISUOG criteria, EFW <3rd percentile was the most prevalent component in our sample. It was recorded in 85% of those identified as FGR according to ISUOG criteria. Moreover, we found that AC had good predictive value for ANO with best cut-off criterion is <3rd centile with a sensitivity of 66.6% and specificity of 90.9%. The EFW had poor predictive value with the best cut-off criterion is <3rd centile had a sensitivity of 85.7% and specificity of 52.9%.

In their meta-analysis Blue et al., [15] found that after 24 weeks gestation AC and EFW < 10th percentile had similar ability to predict SGA. While, Baschat and Weiner found that AC percentile had the highest sensitivity (98.1%) for the diagnosis of FGR when compared with either estimated fetal weight (85.7%) or UA S/D ratio (67.3%) [16].

According to Marchand et al., [17] AC was proved to be the most suitable sonographic parameter in predicting FGR, especially in advanced weeks of gestation, as it reflects the size of the liver, which is affected early in the process of growth retardation due to glycogen depletion. It correlates with the degree of fetal malnutrition. Thus, it has the highest sensitivity for diagnosing FGR.

Abdominal circumference less than 3rd percentile rather than the 10th percentile was a good predictor of composite ANO according to Lees et al. [18].

Unterscheider and his colleagues, [19] found that all fetuses with an EFW less than 3rd centile were at increased risk for either adverse perinatal outcome or NICU admission. In the same line, a large retrospective cohort study, found that the risk of stillbirth was inversely proportional to the percentile of birthweight for gestational age. The risk for stillbirth in those <3rd percentile was as high as 58 per 10,000 at-risk fetuses, and 26.3 for <10th percentile compared to 5.1 for non-SGA gestations [20].

In the era of molecular medicine, different biomarkers were investigated for predicting pre-eclampsia, FGR and stillbirth such as microRNAs, endothelial progenitor cells (EPCs) and natural killer (NK) cells with promising results [21,22]. These advances can be used for future verification of ISUOG criteria for FGR identification.

The main limitation of our study was the relatively small sample size, and the use composite adverse neonatal outcomes instead of individual components as outcomes such as IVH, neonatal anemia, NEC, neonatal seizures or stillbirth because they were rare or absent. Moreover, NICU admission policies as regard the age of viability were major obstacles in studying early-onset FGR.

A main strength of this study is that ISUOG adopted a definition obtained through a Delphi procedure that is usually useful in topics that cannot be answered by clinical research through a series of sequential rounds of questions to reach consensus between a panel of experts, yet; it might introduce new definition parameters based on opinions into clinical practice. So, this study was an attempt to provide evidence to support ISUOG definition.

Conclusions:

As evident from the current study, ISUOG definition for fetal growth restriction can accurately identify fetuses at risk of adverse perinatal outcomes.

Declarations:

Authors' contributions:

M.H was responsible for Data curation, Formal Analysis, Investigation, Writing – review & editing.; G.E contributed in Conceptualization, Formal Analysis, Methodology, , Writing – review & editing.; M.S was responsible for Conceptualization, , Methodology, Resources, , Supervision, Validation, Visualization, Writing – review & editing ; and R.A contributed in Conceptualization, , Methodology, Resources, , Supervision, Validation, Visualization, Writing – original draft.

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Disclosure of interests:

The authors declare that they have no competing interests.

***Ethics approval*:**

The study was approved by the Ethical and Research Committee of the Council of Obstetrics and Gynecology Department, Faculty of Medicine Ain Shams University Ethical Research Committee

(FMASU ERC) (FMASU MS 254/2021) on 17/4/2021 and Ethical Committee of the Council of Obstetrics and Gynecology Department and an informed consent was obtained from all subjects involved in the study.

Informed consent:
Informed consent for data collection for research purposes was obtained from all subjects involved in the study.

Data availability statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1: baseline demographic and clinical criteria

variable		FIGO definition		P value
		FGR (40)	No FGR (15)	
Maternal age		28.42±5.77	29.6±7.57	0.54
Parity	primiparous	15(27.3%)	4(7.3%)	0.452
	multiparous	25(45.5%)	11(20.0%)	
Birth weight		1927.62±603.15	2552.0±287.77	<0.001*
Birth weight z score		-3.71±2.25	-1.44±0.636	<0.001*
pregnancy induced disorders				
No		21(38.2%)	8(14.5)	0.645
Preeclampsia with severe features		15(27.3%)	6(10.9%)	
Preeclampsia with no severe features		1(1.8%)	1(1.8%)	
Gestational HTN		3(5.5%)	0(0)	
past medical disorders				
No		33(60.0%)	11(20.0%)	0.275
APAS		2(3.6%)	0(0)	
Chronic HTN		1(1.8%)	2(3.6%)	
Pregestational DM		1(1.8%)	1(1.8%)	
Epilepsy		2(3.6%)	0(0)	
Asthma		0	1(1.8%)	
HBV		1(1.8%)	0(0)	

*statistical significance, APAS: antiphospholipid syndrome, HTN: hypertension, DM: diabetes mellitus, HBV: hepatitis B viral infection

Table II: different sonographic parameters in the studied cases:

Variables	FGR		no FGR		P value	CI 95%	
	Mean	SD	Mean	SD		lower	upper
HC	295.05	29.52	322.40	10.26	0.001*	-43.07	-11.62
HC percentile	14.33	17.72	35.66	19.21	0.000*	-32.38	-10.27
AC	268.179	32.57	304.6	12.87	0.000*	-53.88	-18.95
AC percentile	4.231	5.5034	12.867	7.9988	0.000*	-12.46	-4.811
FL	63.949	7.2799	69.467	3.3138	**0.007***	-9.4542	-1.5817
FL percentile	23.263	24.885	39.067	27.295	**0.048***	-31.45	-0.1504
EFW	**1955.25**	549.89	**2594.13**	254.043	0.000*	-936.10	-341.65
EFW percentile	1.575	1.6154	5.267	2.0862	0.000*	-4.7557	-2.6276
UAPI	1.1385	0.3924	0.8967	0.08950	0.022*	.03550	.44816
UPI percentile	75.18	28.63	58.73	17.742	0.043*	0.53	32.35
UA RI	0.67	0.146	0.60	0.068	0.174	-0.032	0.173
MCA PI	1.4493	0.2642	1.5533	0.12952	0.266	-.29087	0.08278
MCAPI percentile	23.536	22.473	35.000	8.8176	0.147	-27.165	4.2368

*statistical significance, HC: head circumference, AC: abdominal circumference, FL: femur length, EFW: estimated fetal weight, UAPI: umbilical artery pulsatility index, UA RI: umbilical artery resistance index, MCA PI: middle cerebral artery pulsatility index

Table III: the relationship between FGR using new definition and neonatal outcomes

Neonatal outcome		According to new definition		P value
		FGR	No FGR	
Composite adverse outcome	Yes	21(38.2%)	0 (0)	<0.0001*
	No	19(34.5%)	15(27.3%)	
Respiratory distress syndrome	Yes	20(36.4%)	0 (0)	0.001
	No	20(36.4%)	15(27.3%)	
Neonatal death	Yes	6(10.9%)	0 (0)	0.112
	No	34(61.8%)	15(27.3%)	
Neonatal ICU admission	Yes	21(38.2%)	0 (0)	<0.001*
	No	19(34.5%)	15(27.3%)	
SGA neonate	Yes	38(69.1%)	8 (14.5%)	0.01*
	No	2(3.6%)	7(12.7%)	

% within total sample used for validation

*statistical significance

Figure (1): ROC curve for prediction of ANO using EFW centile'

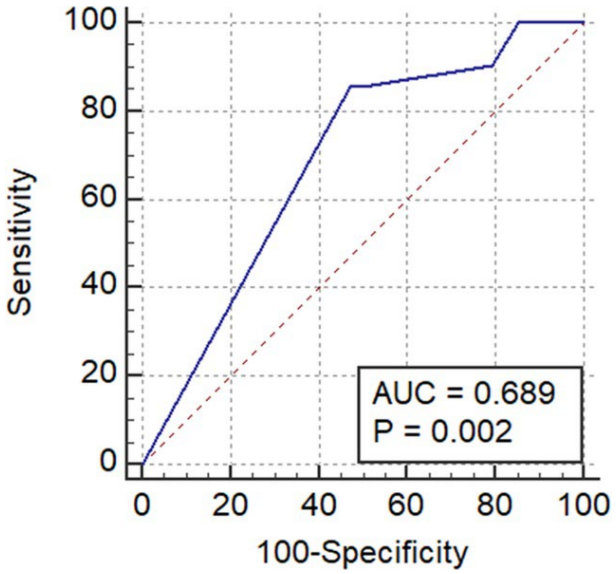

Figure (2): ROC curve for prediction of ANO using AC centile'

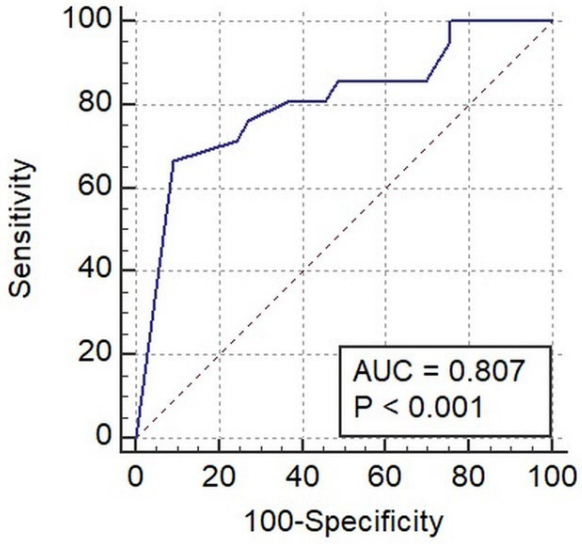

Figure (3): ROC curve for prediction of ANO using umbilical artery PI percentiles