

Prediction of Large for Gestational Age by Ultrasound at 35 Weeks and Impact of Ultrasound-Delivery Interval: Comparison of 6 Standards

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Keywords

Adverse perinatal outcomes · Large for gestational age · Birth weight · Estimated fetal weight · Estimated percentile weight · Fetal growth standard · INTERGROWTH-21st · Ultrasound · WHO fetal growth charts

Abstract

Objective: The aim of the study was to assess the predictive ability of the ultrasound estimated percentile weight (EPW) at 35 weeks to predict large for gestational age (LGA) at term delivery according to 6 growth standards, including population, population-customized, and international references. The secondary objectives were to determine its predictive ability to detect adverse perinatal outcomes (APOs) and whether the ultrasound-delivery interval influences the detection rate of LGA newborns. **Methods:** This was a retrospective cohort study of 9,585 singleton pregnancies. Maternal clinical characteristics, fetal ultrasound data obtained at 35 weeks, and pregnancy and perinatal outcomes were used

to calculate EPWs to predict LGAs at delivery according to the customized and the non-customized (NC) Miguel Servet University Hospital (MSUH), the customized Figueras, the NC Fetal Medicine Foundation (FMF), the NC INTERGROWTH-21st, and the NC World Health Organization (WHO) standards. **Results:** For a 10% false-positive rate, detection rates for total LGAs at delivery ranged from 31.2% with the WHO (area under the curve [AUC] 0.77; 95% confidence interval [CI], 0.76–0.79) to 56.5% with the FMF standard (AUC 0.85; 95% CI, 0.84–0.86). Detection rates and values of AUCs to predict LGAs by ultrasound-delivery interval (range 1–6 weeks) show higher detection rates as the interval decreases. APO detection rates ranged from 2.5% with the WHO to 12.6% with the Figueras standard. **Conclusion:** The predictive ability of ultrasound estimated fetal weight at 35 weeks to detect LGA infants is significantly greater for FMF and MSUH NC standards. In contrast, the APO detection rate is significantly greater for customized standards. The shorter ultrasound-delivery interval relates to better prediction rates.

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Introduction

Screening for fetal growth abnormalities is an essential component of antenatal care, and fetal ultrasound plays a key role in this issue. Greater perinatal morbidity has been observed in large for gestational age (LGA) newborns [1] and stillbirth [2]. ISUOG Practice Guidelines for ultrasound assessment of fetal growth consider LGA fetuses as those with an estimated fetal weight (EFW) above the 90th centile, although the 95th centile, 97th centile, +2 standard deviations, and Z-score deviation have also been referred as cutoffs in the literature [3]. A randomized controlled trial published in 2015 showed that labor induction may decrease perinatal morbidity in newborns weighing more than 4,000 g or above the 95th percentile [4], thus the clinical interest in the early detection of LGAs. In addition, as has been suggested, universal versus selective LGA screening in the 3rd trimester improves the detection rate at delivery [5].

Since ultrasound assessment allows professionals to monitor intrauterine growth, different fetal growth standards have been based on the EFW to calculate the estimated percentile weight (EPW) using Hadlock et al.'s [6, 7] methodology or more recent studies that apply multi-level models. Although studies such as the one conducted by Gardosi et al. [8] have claimed that these standards can also be customized to maternal and fetal physiological variables, other studies have questioned the validity of customized standards [9, 10]. Moreover, international population standards have recently been published by EFW [11], including those from the INTERGROWTH-21st project [12, 13] and the World Health Organization (WHO) [14].

In order to provide new knowledge on the performance of growth standards, the main objective of this study was to compare 6 growth standards, customized and non-customized (NC), local and international ones, to detect LGA in term newborns by ultrasound at 35 weeks. With the same purpose, the secondary objective was to determine the predictive ability to detect adverse perinatal outcomes (APOs) and whether the ultrasound-delivery interval influences the detection rate of LGA newborns.

Methods

Study Design

This was a retrospective cohort study of births assisted at the Miguel Servet University Hospital (MSUH) between March 2012 and December 2016. The inclusion criteria were as follows: (1) live singleton pregnancies controlled in MSUH from the 1st trimester

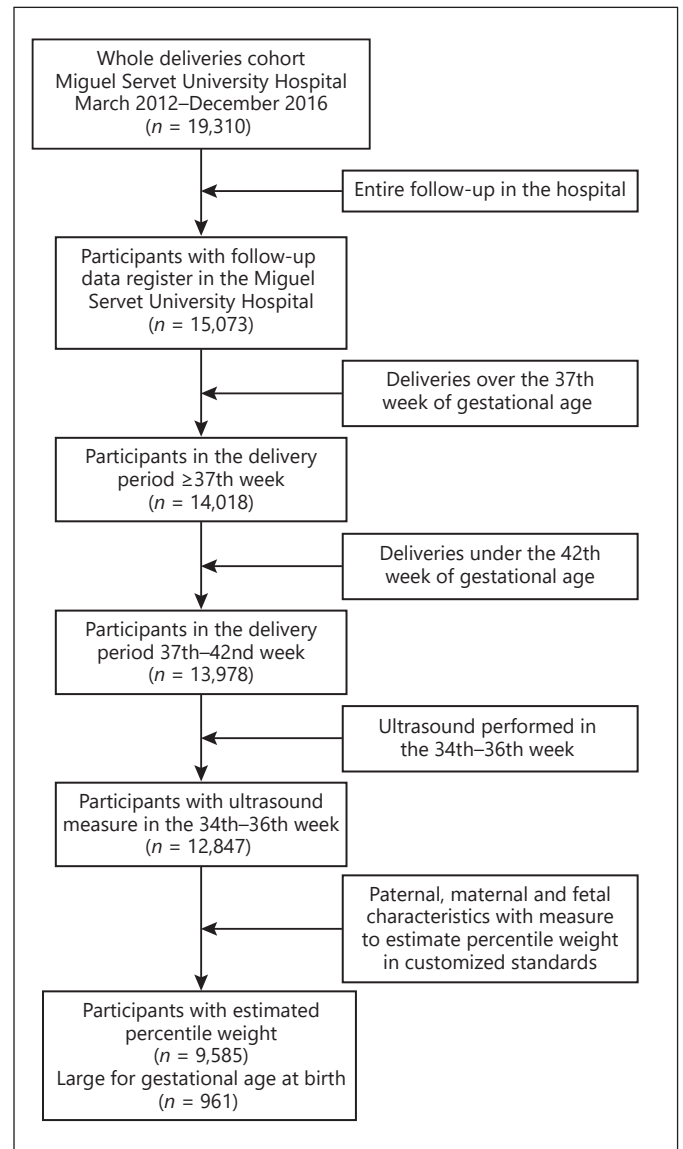


Fig. 1. Flowchart of patient recruitment.

of gestation, (2) fetal ultrasound assessment at a gestational age of 35 (range 34–36) weeks, and (3) deliveries between 37 and 42 weeks of gestational age with fetuses without stillbirth associated with malformations or chromosomal abnormalities. From the 19,310 consecutive deliveries assisted in our hospital in the period studied, the 9,585 cases which fulfilled the specific inclusion criteria such as data availability to estimate percentile weights by standards were considered for the analysis. Selection of study participants is detailed in Figure 1. Our research was approved by the Clinical Research Ethics Committee of Aragón (PI20/414).

The last menstrual period was adjusted by means of 1st trimester ultrasound results [15]. Universal ultrasound screening was performed at 35 weeks (range 34–36 weeks) at the Ultrasound and Prenatal Diagnosis Unit using either Voluson 730 Expert, E6, E8 (General Electric Healthcare, Zipf, Austria) or Aloka ProSound

Table 1. Parental baseline characteristics (top), and pregnancy (middle) and perinatal characteristics (bottom) of pregnancies

Clinical characteristic	Pregnancies (<i>n</i> = 9,585)
<i>Parental characteristic</i>	
Maternal age, years	33.3 (30.1–36.1)
Maternal BMI, kg/m ²	23.2 (21.1–26.2)
Maternal height, cm	163 (159–168)
Paternal height, cm	176 (172–181)
Parity	
0	5,077 (53.0%)
1	3,724 (38.9%)
≥2	784 (8.1%)
Maternal ethnicity	
Caucasian	9,243 (96.4%)
Asian	110 (1.1%)
African	232 (2.4%)
Maternal smoking habits	
Yes	1,546 (16.1%)
No	8,039 (83.9%)
<i>Ultrasound parameters at 35 (34–36) weeks</i>	
Gestational age (weeks) at ultrasound	35.1 (35.0–35.3)
EFW, g by Hadlock	2,495 (2,314–2,697)
EFW, g by Stirnemann	2,421 (2,209–2,648)
Percentile by standard	P50 (P10–P90)
NC MSUH	52.6 (11.9–93.3)
Customized MSUH	52.9 (12.2–92.9)
Figueras	59.3 (18.1–93.5)
INTERGROWTH-21st	51.9 (12.7–89.8)
WHO	43.1 (7.5–74.9)
FMF	37.6 (2.7–89.9)
<i>Pregnancy and perinatal outcomes</i>	
Gestational age at delivery, weeks	40.0 (39.1–40.7)
Newborn gender	
Female	4,652 (48.5%)
Male	4,933 (51.5%)
Birth weight, g	3,310 (3,030–3,590)
LGA	961 (10.02%)
Data are reported as <i>n</i> (%) or median (interquartile range). MSUH, Miguel Servet University Hospital; WHO, World Health Organization; NC, non-customized; FMF, Fetal Medicine Foundation; EFW, estimated fetal weight.	

SSD-5000 (Hitachi Aloka Medical Systems, Tokyo, Japan) ultrasound machines. EFW was calculated with the formula of each model developed using the formula of Hadlock et al. [7] with biparietal diameter, cephalic and abdominal circumference, and femur length for the MSHU, Figueras et al. [16], WHO standards; cephalic and abdominal circumference, and femur length for the Fetal Medicine Foundation (FMF) standard. In addition, for the same reason, Stirnemann et al.'s [12] formula, which considers only cephalic and abdominal circumference, was used to estimate percentile weight for INTERGROWTH-21st.

The variables included in the study were maternal age and BMI at the beginning of pregnancy, parity, maternal and paternal height, maternal ethnic origin, smoking habits, infant gender, birth weight, and ultrasound EFW. We also collected perinatal outcomes to analyze APOs in LGAs at delivery, defined as the oc-

currence of 5-min Apgar score <7, instrumental or cesarean delivery for non-reassuring fetal status (NRFS), arterial cord blood pH < 7.10, and stillbirth.

Estimated Percentile Weight

EPWs were calculated according to 6 different customized and NC growth standards including population, population-customized, and international references. For the customized charts, Hadlock et al.'s [6] and Gardosi et al.'s [8] methodologies were used to develop (1) the MSUH standard customized for parity, age, BMI and maternal height, paternal height, and fetal gender, built using a modified version of Hadlock et al. [6, 7] growth charts adjusted to our population with a coefficient of variation that changes with gestational age (Savirón-Cornudella et al. [17]); (2) and the Barcelona Clinic Hospital (Figueras et al. [16]). For the NC standards,

Table 2. Diagnosis of APOs

	5-min Apgar score <7	Instrumental delivery for NRFS	Cesarean delivery for NRFS	Arterial cord blood pH <7.10	Stillbirth	Any APO
Total cohort	42	161	265	254	19	645
LGA, n (%)	1 (2.4)	13 (8.1)	17 (6.4)	16 (6.3)	1 (5.3)	44 (9.5)
<i>EPW > 90, n (%)</i>						
NC MSUH	4 (9.5)	11 (6.8)	33 (12.5)	25 (9.8)	3 (15.8)	67 (10.4)
Customized MSUH	4 (9.5)	16 (9.9)	37 (14.0)	30 (11.8)	3 (15.8)	79 (12.2)
Figueras	5 (11.9)	16 (9.9)	36 (13.6)	34 (13.4)	4 (21.1)	81 (12.6)
INTERGROWTH-21st	3 (7.1)	8 (5.0)	25 (9.4)	17 (6.7)	2 (10.5)	50 (7.8)
WHO	0 (0)	6 (3.7)	6 (2.3)	4 (1.6)	0 (0)	16 (2.5)
FMF	3 (7.1)	9 (5.6)	27 (10.2)	17 (6.7)	2 (10.5)	52 (8.1)

APOs, adverse perinatal outcomes; NC, non-customized; MSUH, Miguel Servet University Hospital; FMF, Fetal Medicine Foundation; NRFS, non-reassuring fetal status.

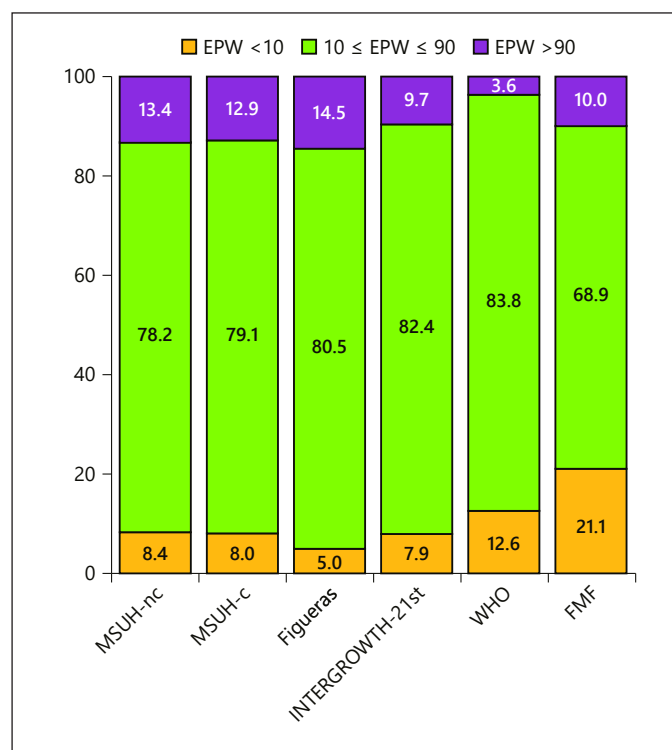


Fig. 2. Bar diagram of percentages of small for gestational age (Orange), adequate for gestational age (Green), and LGA (Purple) provided by standards at 3rd trimester ultrasound (range 34–36 weeks). FMF, Fetal Medicine Foundation; MSUH, Miguel Servet University Hospital; WHO, World Health Organization; LGA, large for gestational age; EPW, estimated percentile weight.

we used (iii) a NC version of the MSUH standard (Savirón-Cornudella et al. [17]); (4) the international population INTERGROWTH-21st [12, 13], a multilevel mixed model which includes pregnant women without any pathology; (5) the international

WHO fetal growth standard [14]; and (6) the FMF local growth multilevel mixed model (Nicolaidis et al. [18]).

To assess ultrasound weight measures in the 3rd trimester, EPWs were estimated between 34 and 36 weeks of gestational age. The WHO EPW was calculated by interpolation of 5, 10, 25, 50, 75, 90, and 95 percentiles. As a gold standard for the analysis, LGA was defined as percentile birth weight over 90, using a growth reference for the Spanish population based on 9,362 birth weights [19].

Statistical Analysis

Once the data had been extracted, a descriptive table with the variables by ultrasound and at delivery was created. The predictive ability of EPW provided by the 6 standards used to predict LGAs was analyzed using the area under the receiver-operating characteristic curve (AUC) [20]. Sensitivity (detection rate) was established for false-positive rates (FPRs) of 5, 10, 15, and 20%. The percentile threshold point corresponding to the FPR values was also calculated. AUCs were compared using the DeLong test and sensitivities through a proportion comparison test. In addition, a sub-analysis was performed using a logistic regression model to estimate the odds ratio (OR) and 95% confidence interval (CI) for an increase in 1% of the EPW at 35 weeks as a predictor for LGAs at delivery, performing a subclassification for different ultrasound-delivery intervals (1–6 weeks).

We analyzed the diagnostic ability of the standards using EPW > 90, and LGA birth weights to detect APOs: 5-min Apgar score <7, instrumental delivery for NRFS, cesarean delivery for NRFS, arterial cord blood pH < 7.10, and stillbirth. Comparison between APOs predicted by standards was performed using a proportion test. The analyses were performed using R version 3.6.1 language programming (R Foundation for Statistical Computing, Vienna, Austria) [21].

Results

Descriptive Results

Table 1 shows the descriptive characteristics of the subjects and displays medians and interquartile ranges

Table 3. Area under the receiver-operating characteristic curve and sensitivity analyses to detect LGA newborns, using EPW by ultrasound at 35 weeks (range 34–36 weeks) for different FPR percentages

Standard	AUC (95% CI)	Sensitivity (95% CI) and threshold percentile points ^a			
		FPR 5%	FPR 10%	FPR 15%	FPR 20%
NC MSUH	0.83 (0.82–0.85)	42.5 (39.3–45.7) (Thr 94.2)	55.8 (52.6–58.9) (Thr 88.6)	66.8 (63.7–69.8) (Thr 83.6)	73.8 (70.8–76.5) (Thr 78.3)
Customized MSUH	0.80 (0.78–0.81)	30.0 (27.1–33.0) (Thr 95.0)	45.3 (42.1–48.5) (Thr 89.5)	55.2 (51.9–58.3) (Thr 84.3)	62.7 (59.6–65.8) (Thr 79.2)
Figueras	0.81 (0.79–0.82)	32.3 (29.3–35.3) (Thr 95.4)	48.4 (45.2–51.6) (Thr 90.5)	58.4 (55.2–61.5) (Thr 86.1)	64.4 (61.3–67.4) (Thr 81.8)
INTERGROWTH-21st	0.84 (0.82–0.85)	36.3 (33.3–39.5) (Thr 91.5)	51.0 (47.8–54.2) (Thr 85.9)	62.0 (58.9–65.1) (Thr 80.1)	72.1 (69.1–74.9) (Thr 75.3)
WHO	0.77 (0.76–0.79)	25.9 (23.2–28.8) (Thr 81.9)	31.2 (28.3–34.3) (Thr 74.5)	35.3 (32.3–38.4) (Thr 73.7)	41.7 (38.6–44.9) (Thr 72.5)
FMF	0.85 (0.84–0.86)	38.2 (35.1–41.4) (Thr 92.2)	56.5 (53.3–59.7) (Thr 84.2)	65.7 (62.5–68.6) (Thr 76.9)	72.8 (69.9–75.6) (Thr 69.8)

MSUH, Miguel Servet University Hospital; Pc, percentile; WHO, World Health Organization; LGA, large for gestational age; NC, non-customized; FMF, Fetal Medicine Foundation; AUC, area under the curve; FPR, false-positive rate; CI, confidence interval; EPW, estimated percentile weight. ^a Sensitive threshold percentile: point that corresponds to a FPR value.

Table 4. Results of *p* value tests to compare standards: AUC and sensitivities (specificity 90%) to predict LGA, and percentage of APO diagnosis

	Customized MSUH			Figueras			INTERGROWTH-21st			WHO			FMF		
	AUC	sens	APOs	AUC	sens	APOs	AUC	sens	APOs	AUC	sens	APOs	AUC	sens	APOs
NC MSUH	<0.001	<0.001	0.334	<0.001	0.001	0.256	<0.001	0.039	0.121	<0.001	<0.001	<0.001	0.057	0.792	0.178
Customized MSUH				0.002	0.188	0.933	<0.001	0.014	0.009	<0.001	<0.001	<0.001	<0.001	<0.001	0.017
Figueras							<0.001	0.274	0.006	<0.001	<0.001	<0.001	<0.001	<0.001	0.010
INTERGROWTH-21st										<0.001	<0.001	<0.001	<0.001	0.018	0.918
WHO													<0.001	<0.001	<0.001

NC, non-customized; MSUH, Miguel Servet University Hospital; FMF, Fetal Medicine Foundation; WHO, World Health Organization; APO, adverse perinatal outcome; AUC, area under the curve.

among groups for the 6 studied standards for EFWs by ultrasound at 35 weeks (range from 34 + 0 to 36 + 6 weeks) and weights at delivery and EPWs. Both WHO and FMF standards show an underestimation of the expected value by ultrasound (median values 43.1%, interquartile range 7.5–74.9, and 37.6%, interquartile range 2.7–89.9, respectively), and similarly, the Figueras standard shows an overestimation by ultrasound (median values 59.3%, interquartile range 18.1–93.5). EPW distributions are detailed in Figure 2, where a comparison of bar diagrams is shown for each standard. The rate of LGA at birth was 10.0% (*n* = 961). Regarding APOs, Table 2 shows that LGA deliveries include 9.5% (*n* = 44) APOs, 2.4% (*n* = 1) 5-min Apgar score <7, 8.1% (*n* = 13) instrumental deliveries for NRFS, 6.4% (*n* = 17) cesarean deliveries for NRFS, 6.3% (*n* = 16) neonatal acidemia (pH cord blood pH < 7.10), and 5.3% (*n* = 1) stillbirth.

Comparison of Growth Standards

Table 3 displays values of AUCs and sensitivities plus the percentile threshold point for different FPRs to predict LGAs at delivery by ultrasound. For a 10% FPR, the detection rates for LGAs for all the standards ranged be-

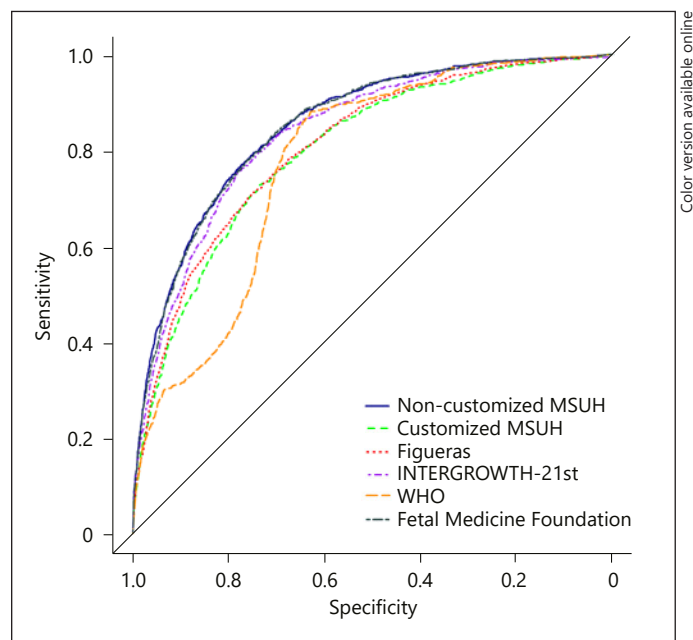


Fig. 3. Receiver-operating characteristic curves: comparison of fetal growth standards for prediction of LGA newborns using EPW by ultrasound at 35 weeks. MSUH, Miguel Servet University Hospital; WHO, World Health Organization.

Fig. 4. ORs and 95% CIs of standards in order to predict LGA newborns according to EPW by ultrasound at 35 weeks. MSUH, Miguel Servet University Hospital; WHO, World Health Organization; ORs, odds ratios; CIs, confidence intervals.

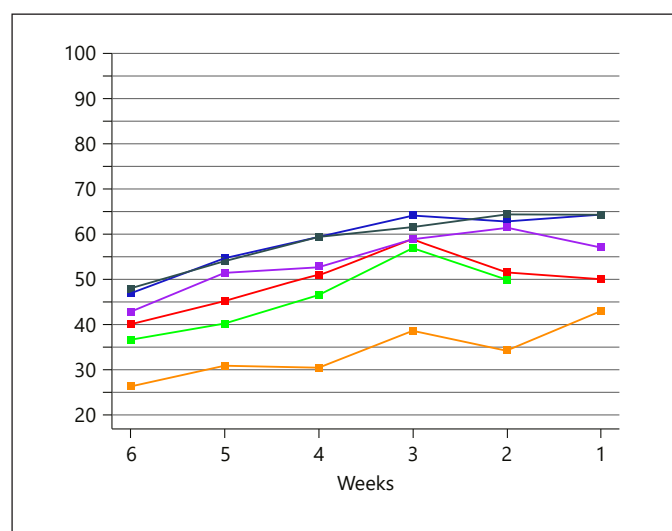
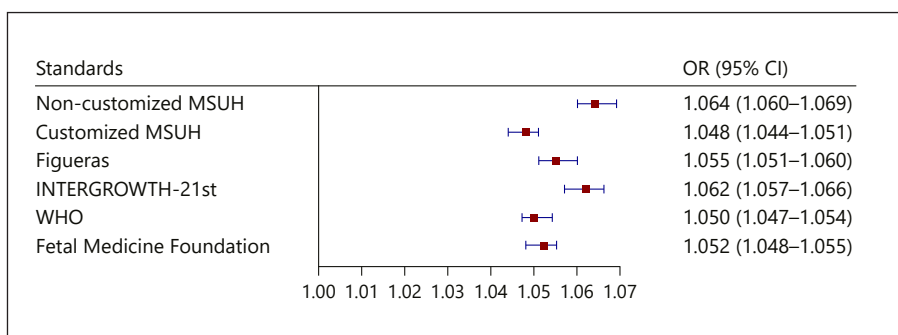


Fig. 5. Prediction of LGA cases by standards by ultrasound-delivery interval (1–6 weeks) for a 10% FPR. Growth standards: NC MSUH [17] (dark blue line), customized MSUH [17] (green line), Figueras et al. [16] (red line), INTERGROWTH-21st [13] (purple line), WHO [14] (orange line), and FMF [18] (dark slate grey line). LGA, large for gestational age; NC, non-customized; MSUH, Miguel Servet University Hospital; WHO, World Health Organization; FMF, Fetal Medicine Foundation; FPR, false-positive rate.

tween 31.2% with the WHO standard (AUC 0.77; 95% CI, 0.76–0.79) and 56.5% with the FMF standard (AUC 0.85; 95% CI, 0.84–0.86). These values were obtained with percentile threshold points over 88.6, 89.5, 90.5, 85.9, 74.5, and 84.2% for, respectively, NC and customized MSUH, Figueras, INTERGROWTH-21st, WHO, and FMF standards. For a 20% FPR, the detection rates ranged from 41.7 to 73.8%, using 78.3, 79.2, 81.8, 75.3, 72.5%, and 69.8% as the percentile threshold points.

Figure 3 illustrates the receiver-operating characteristic curve comparison and the AUC for the prediction of

LGAs at delivery by ultrasound at 35 weeks. Figure 4 displays the results of the logistic regression model with the ORs and 95% CIs to predict LGAs by ultrasound at 35 weeks according to the standards. Online suppl. Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000510020) shows the concordance between predicted LGAs at delivery by standards using EPW > 90.

p Values of the comparisons of the standard AUC values and sensitivity for a 90% specificity are shown in Table 4. The FMF and the NC MSUH standards showed no statistically significant differences between them, but with greater LGA prediction ability than INTERGROWTH-21st, Figueras, and WHO standards. Besides, in the comparison, INTERGROWTH-21st showed significant differences from customized MSHU and WHO standards, but not with the Figueras standard. Finally, customized standards did not show differences between them, but with greater LGA prediction ability than the WHO standard.

Regarding APO prediction by EPW > 90, in Table 2 we show that the customized Figueras and the MSUH standards reached the greatest detection rate, 12.6 and 12.2%, respectively. No statistically significant difference was detected with the NC MSUH (10.4%), although the differences with the FMF (8.1%), INTERGROWTH-21st (7.8%), and WHO (2.5%) standards were significant. The instrumental deliveries for NRFS, cesarean deliveries for NRFS, and neonatal acidemia APOs might explain those differences. *p* values of all comparisons are illustrated in Table 4.

Comparison of Growth Standards by Ultrasound-Delivery Interval

Online suppl. Table 2 displays values of AUCs and sensitivities for different FPRs to predict LGAs by ultrasound-delivery interval (range 1–6 weeks). Figure 5 shows the prediction of LGA cases by standard by ultrasound-delivery interval (1–6 weeks) for a 10% FPR. The ob-

served results show higher detection rates as the interval decreases. Online suppl. Figure 1 illustrates the receiver-operating characteristic curve comparison of fetal growth standards for the prediction of LGA newborns according to the ultrasound-delivery interval (range 1–6 weeks). Online suppl. Figure 1 displays ORs and 95% CIs of standards in order to predict LGAs by ultrasound-delivery interval (range 1–6 weeks).

Discussion

Principal Findings

Our study has demonstrated the utility of EPW by ultrasound exam at 35 weeks (range 34 + 0 to 36 + 6 weeks) as a predictor of LGAs at delivery at term with any model studied. The comparison of 6 growth standards showed similar good predictive ability for LGAs, and with the exception of the WHO standard, NC standards present a greater predictive ability to detect LGAs at delivery. The NC MSHU and FMF standards fit better to a 10% detection of LGAs at delivery and with an ultrasound-delivery interval of 1 week; therefore, MSHU and FMF standards have a higher detection rate. On the contrary, when we analyzed LGAs with the APO predictive ability of the 6 standards by percentile weight >90 at the 35th week of gestational age, customized Figueras and MSUH standards showed the greatest diagnostic ability, with statistically significant differences with 3 of the 4 NC models. A previous study did not find any significant difference between customized and NC standards analyzing the predictive ability of EPW to detect APOs; by contrast, using EPW >90, we detected significant differences [9]. The shorter ultrasound-delivery interval is related to better prediction rates with all the standards.

The predictive capacity for LGAs at delivery was not perfect for the 6 growth standards however, and several studies of ultrasound accuracy have consistently reported an EFW underestimation in LGAs due to the intrinsic error of ultrasound [22], which could, at least partially, justify these detection rates. Lowering the percentile threshold point by ultrasound would, in our view, improve the detection of LGAs at delivery but would increase FPRs. In any case, unless the birth is scheduled, it will be difficult to identify the best time to perform the ultrasound.

Prediction of LGAs at Delivery by Ultrasound

Sovio et al. [5] in 2018 supported universal 36-week ultrasound versus selective scans to screen for LGA in-

fants, with an improvement in detection rates from 27% (FPR 1.7% and AUC 0.71) to 38% (FPR 3.2% and AUC 0.87). Their study included preterm deliveries and a low rate of LGAs of 4.6%, which could explain the lower FPR in their study.

In 2012, Zhang et al. [23] showed a higher predictive ability for LGA infants when an ultrasound was performed close to delivery (AUC 0.843 at 33 weeks and AUC 0.889 at 37 weeks). Souka et al.'s [24] 2013 study reported a 53% detection rate (FPR 10% and AUC 0.85) by ultrasound at 32–33 weeks, which increased to 63% (FPR 10% and AUC 0.87) by ultrasound at 35–36 weeks. Their study matched our results, although it is based on different inclusion criteria (LGA infants defined as higher than the 95 percentile). This is probably because the fetus has less time to modify its weight percentile until birth as the ultrasound-delivery interval decreases.

In a similar line, a longitudinal cohort study by Tarca et al. [25], carried out in 2016, displayed a detection rate of 54% of LGA infants (FPR 10% and AUC 0.84). A possible reason for their lower detection rates might be associated to the earlier ultrasound at 34 weeks. Frick et al. [26] also published similar results scanning at 30–34 weeks with a 41.3% detection rate (FPR 10% and AUC 0.760), which increased to 48.6% at 35–37 weeks (FPR 10% and AUC 0.803). Their work considered maternal factors and also emphasized that the ability to predict increases in LGA infants when estimation of weight assessment was performed closer to delivery.

We could argue that the cutoff point of the 90th percentile by ultrasound seems to be limited to the prediction of LGAs at delivery. Screening by maternal factors and biomarkers in the 3 trimesters of pregnancy has been developed for LGA neonates similar to SGA standards, but with limited results [25]. Understandably, further studies should be conducted which can improve the detection rate of LGAs.

Strengths and Limitations of the Study

As one of the strengths of our research, we should highlight the large sample size of the data analyzed, approximately 10,000 pregnancies. It is also noteworthy that our statistical approach and comparison present a low risk of bias. However, among the limitations of our research, we should mention the fact that our study is restricted to 1 population with a high proportion of Caucasians (96.4%), and our results might therefore show a risk of bias due to the retrospective nature of the study. Hence, future studies might benefit from a more detailed prospective protocol.

Clinical Relevance

The predictive ability of ultrasound EFW at 35 weeks for LGA infants is similarly good for the 6 growth standards, despite the significant improvement detected in the use of NC local or international standards with no statistically significant differences between them. In contrast, when focusing on the use of EPW > 90 at week 35 for the prediction of LGAs with APOs, customized standards demonstrated an advantage over NC standards. We would thus conclude that standards with a shorter ultrasound-delivery interval would be related to better prediction rates.

Acknowledgements

We gratefully thank all the staff of the Ultrasound and Prenatal Diagnosis Unit of the MSUH (Zaragoza, Spain) for their help in the compilation and management of the data, and Concepción Orna for her help in language editing.

Statement of Ethics

The research presented in the manuscript was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and the appropriate guidelines for human studies,

and was approved by the research institute's committee on human research (Clinical Research Ethics Committee of Aragon PI20/414). No patient consents were required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The study has no financial support.

Author Contributions

R.S.C., L.M.E., and R.A.G. contributed to the conception of the study. R.S.C., L.M.E., F.R.P.L., B.C.L., and M.T.D. contributed to the design of the work. P.D.P. and M.T.D. carried out data acquisition. L.M.E., R.A.G., and G.S. performed statistical analyses. All authors were involved in the interpretation of the study results, and the drafting and revision of the manuscript, and all approved the final version to be published.

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