

Identification of large-for-gestational age fetuses using antenatal customized fetal growth charts: Can we improve the prediction of abnormal labor course?

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ABSTRACT

Introduction: Fetal overgrowth is an acknowledged risk factor for abnormal labor course and maternal and perinatal complications. The objective of this study was to evaluate whether the use of antenatal ultrasound-based customized fetal growth charts in fetuses at risk for large-for-gestational age (LGA) allows a better identification of cases undergoing caesarean section due to intrapartum dystocia.

Material and methods: An observational study involving four Italian tertiary centers was carried out. Women referred to a dedicated antenatal clinic between 35 and 38 weeks due to an increased risk of having an LGA fetus at birth were prospectively selected for the study purpose. The fetal measurements obtained and used for the estimation of the fetal size were biparietal diameter, head circumference, abdominal circumference and femur length, were prospectively collected. LGA fetuses were defined by estimated fetal weight (EFW) >95th centile either using the standard charts implemented by the World Health Organization (WHO) or the customized fetal growth charts previously published by our group. Patients scheduled for elective caesarean section (CS) or for elective induction for suspected fetal macrosomia or submitted to CS or vacuum extraction (VE) purely due to suspected intrapartum distress were excluded. The incidence of CS due to labor dystocia was compared between fetuses with EFW >95th centile according WHO or customized antenatal growth charts.

Results: Overall, 814 women were eligible, however 562 were considered for the data analysis following the evaluation of the exclusion criteria. Vaginal delivery occurred in 466 (82.9 %) women (435 (77.4 %) spontaneous vaginal delivery and 31 (5.5 %) VE) while 96 had CS. The EFW was >95th centile in 194 (34.5 %) fetuses according to WHO growth charts and in 190 (33.8 %) by customized growth charts, respectively. CS due to dystocia occurred in 43 (22.2 %) women with LGA fetuses defined by WHO curves and in 39 (20.5 %) women with LGA defined by customized growth charts (p 0.70). WHO curves showed 57 % sensitivity, 72 % specificity, 24 % PPV and 91 % NPV, while customized curves showed 52 % sensitivity, 73 % specificity, 23 % PPV and 91 % NPV for CS due to labor dystocia.

Conclusions: The use of antenatal ultrasound-based customized growth charts does not allow a better identification of fetuses at risk of CS due to intrapartum dystocia.

Abbreviations: US, ultrasound; 2D, two-dimensional; 3D, three-dimensional; LGA, large-for-gestational age; CS, caesarean section; EFW, estimated fetal weight; WHO, World Health Organization; SVD, spontaneous vaginal delivery; VE, vacuum extractor; PPV, positive predictive value; NPV, negative predictive value.

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Introduction

Fetal macrosomia is among the acknowledged risk factors for intrapartum dystocia and other major complications of labor for the mother and the fetus which include emergency caesarean section, postpartum hemorrhage, perineal tears, shoulder dystocia and hypoxic-ischemic encephalopathy [1,2].

The ultrasound (US) evaluation of the fetal weight either with two-dimensional (2D) ultrasound (US) [3] or with the more recently described three-dimensional (3D) US techniques [4–8] is currently considered the most accurate method for the antenatal detection of fetal macrosomia, even though US estimation of the fetal size is known to become increasingly imprecise at the extremes of the distribution of the estimated fetal weight and particularly in the setting of suspected fetal overgrowth [9].

Fetal macrosomia has been commonly referred to a birthweight above the threshold of 4000 g [10]. However, it is widely acknowledged that fetal macrosomia does not necessarily lead to cephalo-pelvic disproportion (CPD), which is not determined only by the fetal size but also by the size and the anatomic features of the maternal pelvis [11,12].

Based on the assumption that fetal growth pattern may be subjected to substantial variability related to the race and constitutional characteristics of the parents, over the last two decades the use of customized antenatal growth charts has been proposed in clinical practice with the aim of assessing the specific growth potential of each fetus and to tailor on this the management of pregnancy. However, the clinical usefulness of such approach in improving the pregnancy outcome is still debated. In particular, there is limited data on the performance of customized fetal growth charts within the context of suspected fetal overgrowth and its related complications [13–18]. The aim of this study was to compare the accuracy of recently implemented antenatal ultrasound-based customized growth charts [19] with that of the growth charts developed by the World Health Organization (WHO) [20] in the identification of LGA fetuses undergoing caesarean section (CS) due to intrapartum dystocia.

Methods

The study involved five Italian Tertiary Maternity Units (University Hospitals of Parma, Brescia, Rome Tor Vergata and Naples Federico II and Burlo Garofolo Hospital, Trieste) between January 2017 and July 2018. In the involved centres, all patients with non-anomalous singleton pregnancy and acknowledged risk factors for fetal macrosomia – which included a medical history of pregestational diabetes mellitus, obesity, as defined as body mass index above 30 kg/m² [2], or obstetric risk factors such as gestational diabetes (diagnosed following the Guidelines by the World Health Organization) [21], previous history of fetal macrosomia or suspected fetal macrosomia at US or symphysis-to-fundal height assessment of the fetal growth performed in the third trimester – were referred to a dedicated antenatal clinic for the antenatal US estimation of the fetal weight between 35 and 38 weeks of gestation. Pregnancy dating was derived by first trimester ultrasound. Patients were considered eligible for the study purposes in the absence of any fetal genetic and structural abnormality diagnosed either antenatally or postnatally and in the case of availability of labor and postnatal outcomes.

As per common practice in all the participating referral Fetal Medicine Units prenatal US examinations follow the 2015 Guidelines of the Italian Society on Ultrasound in Obstetrics and Gynecology (SIEOG) [22]. In all cases the antenatal estimation of the fetal weight was performed by maternal-fetal medicine specialists using two-dimensional transabdominal low frequency probes and the EFW was computed according to the Hadlock IV

Model [3], which relies on the combination of the measurements of the biparietal diameter, head circumference, abdominal circumference and femur length. Data were prospectively collected. The EFW percentile was computed according to local charts which were used for the clinical management of each patient.

For the study purposes, the EFW data obtained from each Centre were plotted on the antenatal standard growth charts for the estimation of the fetal weight developed by the WHO [20], while biometry data as well as maternal and paternal characteristics were used to calculate the EFW according to the customized fetal growth charts previously published by the SIEOG [19]. Such charts are based on cross-sectional US measurements from uncomplicated singleton pregnancies, accurately dated by crown-rump length in the first trimester, delivering after 37 weeks' gestation with known outcome and information available on maternal and paternal height and weight, parity, and ethnicity [19]. In details, maternal and paternal characteristics were included in the algorithm used to obtain customized measurements, while the customized EFW was computed by means of the Hadlock III model as previously described [23]. Of note, the absence of any of the covariates included in the customization algorithm precludes to obtain the customized EFW. The 95th percentile of the customized growth chart was derived using the cases from our original manuscript on antenatal ultrasound-based customized growth charts for singletons [19] and, together with the 95th percentile of the WHO growth chart, represented the threshold for the retrospective identification of large-for-gestational age fetuses (LGA) in the study population. This evaluation was used only for the study purposes and had no influence on the clinical management of the patients. As per the aim of the study, we compared labor and postnatal outcomes in fetuses identified as LGA according to the WHO charts and those so defined according to customized charts. In particular, the occurrence of intrapartum dystocia leading to unplanned caesarean section was compared between LGA fetuses according to WHO vs customized charts.

Information concerning maternal age, ethnicity, parity, gestation at the onset of labor and body mass index (BMI) at booking and at delivery were collected from patient notes and recorded. After delivery, intrapartum and neonatal outcome data were collected from patient case notes. Outcome measures included birthweight, the mode of delivery and a series of variables such as epidural, augmentation rate, length of labor, postpartum hemorrhage and third and fourth-degree tear in the mother and birthweight and birthweight centile corrected for gender and parity according to the Italian growth charts published by Bertino et al. [24], rate of shoulder dystocia, APGAR score at 5 min, cord arterial and venous pH, admission to Neonatal Intensive Care Unit (NICU) for the neonate. The decision as to whether to deliver due to suspected intrapartum distress was subjectively defined by the physician in charge for the patient care based on abnormal CTG tracing according to FIGO classification system [25], while the decision to opt for operative delivery due to intrapartum dystocia was based on the recommendations of the American College of Obstetricians and Gynecologists for the safe prevention of the primary caesarean delivery [1]. Deliveries were categorized according to the mode of delivery in spontaneous vaginal delivery (SVD) and obstetric intervention by vacuum extractor (VE) or CS, which were further sub-classified based on the primary indication (i.e. dystocia or distress).

Cases submitted to elective CS for any indication or to induction of labor before 39th weeks due to suspected fetal macrosomia were excluded from data analysis, as were those diagnosed with failed induction, whose diagnostic criteria differed across the participating Centres.

A sample size of 238 patients per group (n = 476 in total) was planned to compare the primary outcome between the two groups.

The sample size estimation was based on recent retrospective data comparing the incidence of emergency CS in fetuses identified as LGA by customized vs reference charts [26]. We assumed that the incidence of unplanned CS for labor dystocia in the control group (i.e. LGA defined by reference charts) would be 42.7 % and that the use of customized antenatal growth charts would be associated with an emergency CS rate increased up to 55.5 %. The sample size was computed using Power and Sample Size Calculator (Biostatistics Department, Vanderbilt University, Nashville, TN, USA) considering an 80 % power and a P-value of 0.05.

As per National regulations, ethics approval for this study was granted by the local ethics committee in all the participating centers.

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 (IBM Inc., Armonk, NY, USA). Comparison of normally and non-normally distributed continuous variables included the T test for independent sample and 2-tailed *t*-test and the Mann-Whitney U-test, respectively and data were shown as mean $\pm$ standard deviation or as median (range) accordingly. Categorical variables were reported as number (percentage) and compared using the Chi-square or Fisher exact test. Sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), positive and negative likelihood ratios (LR + and LR -, respectively) for the identification of cases of CS due to intrapartum dystocia in LGA fetuses identified at reference and customized charts were evaluated and compared. $p < 0.05$ was

considered as statistically significant. This study was reported according to the STROBE guidelines [27].

Results

Overall, 814 women were eligible over the study period, of whom 562 were included for the analysis after the evaluation of the exclusion criteria (Fig. 1).

Table 2
Demographic features of the included cases.

	All cases N 562
Age (years) mean $\pm$ SD	32.4 $\pm$ 5.8
Ethnicity n (%)	White (Caucasian, Arabic) 454 (80.5 %) African 59 (10.7 %) Asian 38 (6.9 %) Other (Caribbean, South American, Mixed) 11 (1.9 %)
Risk factor for fetal macrosomia n (%)	DM/GDM + suspected LGA fetus 124 (22.3 %) DM/GDM + polyhydramnios 4 (0.7 %) DM/GDM + BMI >30 kg/m ² 61 (10.7 %) History of GDM + fetal macrosomia 5 (0.8 %) BMI >30 kg/m ² 179 (32.0 %) Suspected LGA fetus (at US or SFH assessment) 155 (27.5 %) History of fetal macrosomia 34 (6.0 %)
Parity n (%)	Nulliparae 249 (44.9 %)
BMI at conception (kg/m ²) mean $\pm$ SD	28.2 $\pm$ 5.8
Term pregnancy BMI (kg/m ²) mean $\pm$ SD	32.2 $\pm$ 5.2
Gestational age at US examination (weeks ⁺ days ⁻) mean $\pm$ SD	36 ⁺⁵ 0 ⁺⁶
Estimated fetal weight centile at US examination (local chart) mean $\pm$ SD	76.2 $\pm$ 20.2
Gestational age at delivery (weeks ⁺ days ⁻) mean $\pm$ SD	39 ⁺³ 1 ⁺¹
Induction of labor n (%)	249 (45.9 %)
Mode of delivery n (%)	SVD 435 (77.4 %) VE 31 (5.5 %) CS 96 (17.1 %)
Obstetric intervention due to dystocia n (%)	VE 13 (41.9 %) CS 76 (79.2 %)
Shoulder dystocia n (%)	Yes 4 (0.7 %)
Fetal Gender n (%)	Male 316 (56.2 %)
Birthweight (grams) mean $\pm$ SD	3737 $\pm$ 474
Birthweight percentile mean $\pm$ SD	73.0 $\pm$ 24.5
Umbilical artery pH mean $\pm$ SD n = 464	7.26 $\pm$ 0.08
Umbilical vein pH mean $\pm$ SD n = 356	7.34 $\pm$ 0.07
Apgar at 5 mins median (range) n = 554	9 (4–10)
NICU admission n (%)	Yes 8 (1.4 %)
Length of neonatal admission median (range)	2 (1–17)

US: ultrasound.

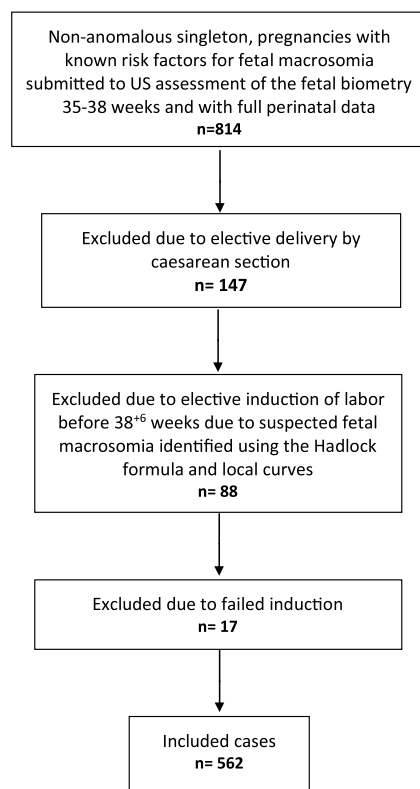


Fig. 1. Flow chart (according to STROBE guidelines) [27] for inclusion of cases.

Table 1
Agreement and disagreement in the identification of LGA fetuses at WHO and customized growth charts.

	Customized <95th percentile n (%)	Customized $\geq$ 95th percentile n (%)
WHO <95th percentile n (%)	349 (62.1 %)	19 (3.4 %)
WHO $\geq$ 95th percentile n (%)	23 (4.1 %)	171 (30.4 %)

Among the included cases, 194 (34.5 %) fetuses had EFW >95th percentile according to WHO charts and 198 (33.8 %) according to customized curves. In 7.5 % of cases (42/562) the WHO and the customized charts yielded discordant results in the identification of LGA (Table 1), with a comparable number of cases that were classified as LGA only by one chart (4.1 % [23/562] for WHO and 3.4 % [19/562] for customized charts, respectively).

Demographic features and perinatal outcomes of the included cases are summarized in Table 2. Within our population of 562 fetuses at risk of macrosomia, vaginal delivery occurred in 466 cases (82.9 %), of which 435 (77.4 %) were SVD and 31 VE (5.5 %), while CS was performed in the remaining 96 cases (17.1 %). In this latter group, intrapartum dystocia represented the leading indication 76 cases (79.2 %).

The birthweight was >95th centile in 103 (18.3 %) neonates. Of these, 66 (64.1 %) and 62 (60.2 %) had been antenatally classified as LGA at WHO and customized charts, respectively ($p = 0.57$).

The perinatal outcomes of fetuses identified as LGA according to WHO and customized antenatal charts are summarized in Tables 3 and 4, respectively. Fetuses identified as LGA at WHO charts showed significantly lower gestational age at scan ($p = 0.01$) and at birth ($p < 0.001$) and had lower augmentation rate ($p = 0.002$), while the frequency of obstetric intervention and CS due to labor dystocia were significantly higher compared to fetuses with EFW <95th percentile ($p < 0.001$ for both), as were the birthweight ($p < 0.001$), the birthweight percentile ($p < 0.001$) and the length

of NICU admission ($p = 0.003$). In fetuses with EFW >95th percentile according to customized growth charts a significantly lower gestational age at scan was also noted ($p < 0.001$); additionally, a significantly lower gestational age at birth and augmentation rate were recorded ($p < 0.001$ for both); finally, the frequency of obstetric intervention and CS due to labor dystocia was significantly higher compared to non-LGA fetuses ($p = 0.001$ and $p < 0.001$, respectively), as were the birthweight ($p < 0.001$), the birthweight percentile ($p < 0.001$) and the length of the neonatal admission to NICU ($p = 0.04$).

The results of the paired comparison of the perinatal outcomes of fetuses identified as LGA at WHO and customized growth charts, respectively, is shown in Table 5. No differences were found between the two groups for any of the evaluated demographic and perinatal outcomes, the rate of obstetric intervention and CS due to intrapartum dystocia. Sensitivity, specificity, PPV and NPV and LR+ and LR- for the identification of cases of CS due to intrapartum dystocia in LGA fetuses identified at WHO and customized charts are summarized in Table 6. Both charts showed low and similar sensitivity [0.57, 95 % CI (0.45 – 0.68) for WHO charts and 0.52, 95 % CI (0.40 – 0.64) for customized, respectively] and specificity [0.72, 95 % CI (0.68 – 0.76) for WHO charts and 0.73, 95 % CI (0.69 – 0.77) for customized charts], with low PPV [0.24, 95 % CI (0.18 – 0.31) for WHO charts and 0.23, 95 % CI (0.17 – 0.30) for customized charts] and LR+ [2.01, 95 % CI (1.57–2.56) and 1.90, 95 % CI (1.47–2.47) for WHO and customized charts, respectively].

Table 3
Perinatal outcomes in normal size vs large-for-gestational age fetuses according to WHO charts.

	EFW <95th percentile WHO chart N 368	EFW >95th percentile WHO chart N 194	p
Gestational age at US examination (weeks [±] days) mean ± SD	36 ⁺⁶ ± 0 ⁺⁵	36 ⁺⁵ ± 0 ⁺⁶	0.01
Gestational age at delivery (weeks [±] days) mean ± SD	39 ⁺⁵ ± 1 ⁺⁰	39 ⁺⁰ ± 1 ⁺²	<0.01
Fetal Gender n (%)	Male 200 (54.3 %)	Male 116 (59.8 %)	0.23
Induction of labor n (%) n = 561	Yes 167 (45.5 %)	Yes 82 (42.3 %)	0.46
Length of labor (minutes) mean ± SD n = 446	283 ± 196	307 ± 224	0.24
Mode of delivery n (%)	SVD 303 (82.3 %)	SVD 132 (68.0 %)	<0.01
	VE 18 (4.9 %)	VE 13 (6.8 %)	
	CS 47 (12.8 %)	CS 49 (25.2 %)	
Mode of delivery – Obstetric intervention due to fetal distress excluded n (%)	SVD 303 (88.1 %)	SVD 132 (73.3 %)	<0.01
	VE 8 (2.3 %)	VE 5 (2.8 %)	
	CS 33 (9.6 %)	CS 43 (23.9 %)	
Birthweight (grams) mean ± SD	3617 ± 468	3957 ± 405	<0.01
Birthweight percentile mean ± SD	65.9 ± 25.9	86.3 ± 14.4	<0.01
Shoulder dystocia n (%)	Yes 3 (0.8 %)	Yes 1 (0.5 %)	0.69
Augmentation n (%)	Yes 147 (48.7 %)	Yes 58 (33.3 %)	<0.01
n = 476			
Epidural n (%)	Yes 124 (52.8 %)	Yes 59 (50.4 %)	0.68
n = 352			
III-IV degree tear n (%)	Yes 6 (1.6 %)	Yes 4 (2.1 %)	0.71
Episiotomy n (%)	Yes 65 (18.1 %)	Yes 46 (24.5 %)	0.08
n = 548			
APGAR 5 < 7 n (%)	Yes 2 (0.6 %)	Yes 1 (0.5 %)	0.96
n = 554			
UA pH mean ± SD n = 464	7.26 ± 0.08	7.25 ± 0.08	0.20
UA pH < 7.10 n (%)	Yes 13 (4.3 %)	Yes 6 (3.7 %)	0.75
n = 464			
NICU admission n (%)	Yes 5 (1.4 %)	Yes 3 (1.7 %)	0.82
N = 523			
Length of neonatal admission (days) median (range)	2 (2–15)	3 (1–17)	<0.01

US: ultrasound.

Table 4

Perinatal outcomes in normal size vs large-for-gestational age fetuses according to customized charts.

	EFW <95th percentile customized chart N 372	EFW ≥95th percentile customized chart N 190	P
Gestational age at scan (weeks ^{+days}) <i>mean</i> + <i>SD</i>	36 ⁺⁶ + 0 ⁺⁵	36 ⁺⁴ + 0 ⁺⁶	<0.01
Gestational age at delivery (weeks ^{+days}) <i>mean</i> + <i>SD</i>	39 ⁺⁵ + 1 ⁺⁰	38 ⁺⁶ + 1 ⁺²	<0.01
Fetal Gender n (%)	Male 206 (55.5 %)	Male 110 (57.9 %)	0.59
Induction of labor n (%)	Yes 166 (44.7 %)	Yes 83 (43.7 %)	0.81
n = 561			
Length of labor (minutes) <i>mean</i> + <i>SD</i> n=446	291 + 202	284 + 226	0.81
Mode of delivery n (%)	SVD 305 (82.0 %) VE 19 (5.1 %) CS 48 (12.9 %)	SVD 130 (68.4 %) VE 12 (6.3 %) CS 48 (25.3 %)	<0.01
Mode of delivery – Obstetric intervention due to fetal distress excluded n (%)	SVD 305 (86.9 %) VE 10 (2.9 %) CS 36 (10.2 %)	SVD 130 (75.6 %) VE 3 (1.7 %) CS 39 (22.7 %)	<0.01
Birthweight (grams) <i>mean</i> + <i>SD</i>	3627 + 470	3931 + 415	<0.01
Birthweight percentile <i>mean</i> + <i>SD</i>	66.0 + 25.9	85.8 + 14.5	<0.01
Shoulder dystocia n (%)	Yes 4 (1.1 %)	Yes 0 (0.0 %)	0.15
Augmentation n (%)	Yes 152 (49.5 %)	Yes 53 (31.4 %)	<0.01
n = 476			
Epidural n (%)	Yes 123 (52.8 %)	Yes 60 (50.4 %)	0.67
n = 352			
III-IV degree tear n (%)	Yes 8 (2.2 %)	Yes 2 (1.1 %)	0.35
Episiotomy n (%)	Yes 67 (18.4 %)	Yes 44 (23.9 %)	0.13
n = 548			
APGAR 5 < 7 n (%)	Yes 1 (0.3 %)	Yes 2 (1.1 %)	0.23
n = 554			
UA pH <i>mean</i> + <i>SD</i> n = 464	7.26 + 0.09	7.26 + 0.08	0.18
UA pH < 7.10 n (%)	Yes 14 (4.6 %)	Yes 5 (3.1 %)	0.43
n = 464			
NICU admission n (%)	Yes 4 (1.1 %)	Yes 4 (2.3 %)	0.31
N = 523			
Length of neonatal admission (days) <i>median</i> (<i>range</i>)	2 (2–9)	3 (1–17)	0.04

Discussion

This study has demonstrated that, within a selected population of pregnant women at risk for fetal macrosomia, the use of customized growth charts compared to standard growth charts does not improve the identification of LGA fetuses who eventually undergo unplanned caesarean section due to intrapartum dystocia. In our cohort, the performance of WHO and customized growth charts was similar in terms of identification of LGA fetuses and the perinatal outcome was also comparable between the two groups.

It is a common ground in obstetrics to assume that the greater the maternal size the lower the likelihood of obstructed labor, irrespective of the actual fetal size. Indeed, the available data suggests a direct relationship between maternal height and size of the birth canal [28–30]. Furthermore, the use of customized growth charts allows to correlate the fetal size to maternal (or parental) characteristics [31–34] and is supposed to define which is the appropriate biometry of a specific fetus in relation to the maternal anthropometric features.

On this basis, it seems tempting to speculate that a fetus appearing large after having adjusted its growth trajectory for maternal (and/or parental) characteristics is expected to be at higher risk of caesarean delivery due to obstructed labor. The background concept is that infants whose size is

disproportionately large for their mothers are at risk of intrapartum and/or perinatal complications.

On the other hand, the results from our multicentric work suggest that customized growth charts are unlikely to be helpful in the prediction of obstructed labor due to CPD nor in the antepartum identification of cases at higher risk of major perinatal complications. Differently from what we expected indeed in the late 3rd trimester the use of Italian customized growth charts built on algorithms which include a series of parental characteristics [19] showed identical performances compared to the recent standard charts developed by the WHO [20]. The decision to adopt these latter charts as the standard reference for comparison was shared among the main study investigators and was based on the robustness and external validity of the data collected by Kiserud et al. [20]. It is unknown whether the comparison of the customized Italian charts with different standard growth chart at 35–37 weeks would have led to different results in terms of identification of LGA newborns and prediction of CS due to obstructed labor.

The evaluation of the role of the customized charts in the identification of fetal overgrowth leading to obstructed labor and its associated perinatal morbidity has so far yielded contradictory results in non-selected as well as in populations at risk of fetal macrosomia. Four studies conducted on non-selected populations

Table 5

Comparison of the perinatal outcomes of fetuses large-for-gestational age fetuses according to WHO versus customized growth charts.

	EFW $\geq$ 95th percentile WHO chart N 194	EFW $\geq$ 95th percentile customized chart N 190	p
Gestational age at scan (weeks ⁺ days) <i>mean</i> $\pm$ <i>SD</i>	36 ⁺⁵ $\pm$ 0 ⁺⁶	36 ⁺⁴ $\pm$ 0 ⁺⁶	0.54
Gestational age at delivery (weeks ⁺ days) <i>mean</i> $\pm$ <i>SD</i>	39 ⁺⁰ $\pm$ 1 ⁺²	38 ⁺⁶ $\pm$ 1 ⁺²	0.59
Fetal Gender n (%)	Male 116 (59.8 %)	Male 110 (57.9 %)	0.70
Induction of labor n (%)	Yes 82 (42.3 %)	Yes 83 (43.7 %)	0.78
n = 561			
Length of labor (minutes) <i>mean</i> $\pm$ <i>SD</i> n=446	307 $\pm$ 224	284 $\pm$ 226	0.45
Mode of delivery n (%)	SVD 132 (68.0 %)	SVD 130 (68.4 %)	0.99
	VE 13 (6.8 %)	VE 12 (6.3 %)	
	CS 49 (25.2 %)	CS 48 (25.3 %)	
Mode of delivery – Obstetric intervention due to fetal distress excluded n (%)	SVD 132 (73.3 %)	SVD 130 (75.6 %)	0.77
	VE 5 (2.8 %)	VE 3 (1.7 %)	
	CS 43 (23.9 %)	CS 39 (22.7 %)	
Obstetric intervention due to dystocia n (%)	Yes 48 (24.7 %)	Yes 42 (22.1 %)	0.54
Caesarean section due to intrapartum dystocia n (%)	Yes 43 (22.2 %)	Yes 39 (20.5 %)	0.70
Birthweight (grams) <i>mean</i> $\pm$ <i>SD</i>	3957 $\pm$ 405	3931 $\pm$ 415	0.72
Birthweight percentile <i>mean</i> $\pm$ <i>SD</i>	86.3 $\pm$ 14.4	85.8 $\pm$ 14.5	0.93
Shoulder dystocia n (%)	Yes 1 (0.5 %)	Yes 0 (0.0 %)	0.32
Augmentation n (%)	Yes 58 (33.3 %)	Yes 53 (31.4 %)	0.70
n = 476			
Epidural n (%)	Yes 59 (50.4 %)	Yes 60 (50.4 %)	0.99
n = 352			
III-IV degree tear n (%)	Yes 4 (2.1 %)	Yes 2 (1.1 %)	0.43
Episiotomy n (%)	Yes 46 (24.5 %)	Yes 44 (23.9 %)	0.90
n = 548			
APGAR 5 < 7 n (%)	Yes 1 (0.5 %)	Yes 2 (1.1 %)	0.55
n = 554			
UA pH <i>mean</i> $\pm$ <i>SD</i> n = 464	7.25 $\pm$ 0.08	7.26 $\pm$ 0.08	0.97
UA pH < 7.10 n (%)	Yes 6 (3.7 %)	Yes 5 (3.1 %)	0.79
n = 464			
NICU admission n (%)	Yes 3 (1.7 %)	Yes 4 (2.3 %)	0.69
N = 523			
Length of neonatal admission (days) <i>median (range)</i>	3 (1–17)	3 (1–17)	0.64

US: ultrasound.

UA: umbilical artery.

UV: umbilical vein.

NICU: neonatal intensive care unit.

Table 6

Sensitivity, specificity, positive and negative predictive values (PPV and NPV), positive and negative likelihood ratios (LR + and LR-) for the identification of cases of caesarean section due to intrapartum dystocia in large-for-gestational age (LGA) fetuses identified at WHO and customized charts.

	EFW $\geq$ 95th percentile WHO chart	EFW $\geq$ 95th percentile customized chart
Sensitivity	0.57, 95 % CI (0.45 – 0.68)	0.52, 95 % CI (0.40 – 0.64)
Specificity	0.72, 95 % CI (0.68 – 0.76)	0.73, 95 % CI (0.69 – 0.77)
PPV	0.24, 95 % CI (0.18 – 0.31)	0.23, 95 % CI (0.17 – 0.30)
NPV	0.91, 95 % CI (0.88 – 0.94)	0.91, 95 % CI (0.87 – 0.93)
LR +	2.01, 95 % CI (1.57–2.56)	1.90, 95 % CI (1.47–2.47)
LR -	1.65, 95 % CI (1.27–2.15)	1.51, 95 % CI (1.19–1.93)

[13,15,16,26] found that customized models based on a previously described algorithm [34] can improve the recognition of LGA populations at risk of intrapartum morbidity, while Sjaarda et al. [18] could not demonstrate in this respect a decisive superiority of customized charts compared with population-based curves. Similar results were found in studies specifically focused on high risk populations. Within a selected cohort of pregnancies

complicated by diabetes, Gonzalez et al. [14] found that the identification of LGA using customized charts was associated with a higher incidence of caesarean sections performed due to intrapartum dystocia, while an earlier study conducted on mothers affected by gestational diabetes could not demonstrate a better identification of LGA neonates at risk of adverse perinatal outcomes compared to population curves [17]. It is important to

note that in all the aforementioned studies the customized models were developed based on a previously described algorithm based on birthweight [34], while the SIEOG customized charts have been developed from cross-sectional ultrasound measurements [19].

The use of customized fetal growth charts in clinical practice is still a matter of controversy. Some have suggested a better performance of the customized approach in the identification of small fetuses at risk of adverse outcomes compared to different local, national or international standards [35–38]. Nevertheless, the rationale behind customized growth charts has been challenged by the recently implemented international growth standards published by the Intergrowth consortium and by the World Health Organization [20,39] and a systematic review of 20 studies failed to demonstrate the superiority of either method in the identification of fetuses at risk for adverse perinatal outcome including mortality [40].

Customization *per se* represents a mathematic algorithm designed in order to adjust the fetal growth trajectory on the basis of the anthropometric characteristics of the parents [19,31–34]. Regarding the possible usefulness of a customized model in predicting the occurrence of cephalopelvic disproportion among LGA infants, the contribution of paternal characteristics is debatable when not difficult to ascertain. Additionally, the currently available customized growth models do not take into account specifically maternal pelvimetry parameters which are related to the woman size but may have an independent major impact on the chance of dystocia leading to obstetric intervention. Among these, a narrow width of the subpubic arch angle (SPA) as a surrogate of a narrow birth canal has been demonstrated by some investigators of our group to be independently associated with the risk of obstructed labor within a selected cohort of nulliparous women with LGA fetuses [12]; of note, in a recent work by Rizzo et al. both fetal HC and SPA were found to be independent risk factors for intrapartum dystocia leading to emergency obstetric intervention [41]. On this ground, we do envisage that it is reasonable to hypothesize that the performance of the customization in predicting the risk of obstructed labor among LGA fetuses can be improved by including pelvimetric parameters in the customization method [18]. Finally, intrapartum fetal head malpositions and malpresentations also represent a major determinant of dystocia leading to caesarean section and this factor is not included – and cannot be included – in any antepartum customized model aiming at the detection of cases at risk of CPD [42–45].

To our knowledge, this is the first study evaluating the role of newly developed ultrasound-derived customized growth charts [19] in the identification of LGA within a population at high risk of fetal overgrowth and to compare their performance to that of recently implemented standard charts [20]. The prospective design of the data collection together with the wide patient sample collected and the strict criteria for the inclusion of the patients are the major strengths of our work. Moreover, in all included units the US estimation of the fetal biometry was performed by Fetal Medicine specialists. Finally, it has to be acknowledged that all the participating centers are tertiary referral hospitals that use shared and internationally acknowledged protocol for the management of labor progression [1]. On the other hand, the fact that each center used local growth standards for the management of the cases at risk of fetal macrosomia and that the policy of induction of labor for suspected macrosomia also differed in the participating units may represent a limitation, however differences in terms of management policy across different Centres are not uncommon in the routine clinical practice. On this basis, 88 cases were excluded due to elective induction of labor for suspected macrosomia before 39⁺⁰ weeks, however we believe

that their inclusion would have biased the validity of our results. Within such context, the paired comparison between the customized and the WHO standards did not yield any “subclinical” difference worth to be investigated on a wider number of cases. Another limitation may be accounted by the method adopted to obtain the EFW from customized US measurements, which may have impacted on the effect of customisation. Furthermore, the decision to use the 95th percentile as the cut-off value for LGA was arbitrary and based on the fact that we aimed to identify the fetuses at highest risk of obstructed labor. Of note, such cut-off value has been extensively used by several Authors and research groups [10,46–49] and has recently been suggested to reduce the likelihood of false-positive cases [47].

In conclusion, our data on a selected cohort of women at risk for fetal macrosomia suggest that the use of newly developed ultrasound-derived customized antenatal growth charts does not improve the identification of LGA infants undergoing intrapartum caesarean section due to suspected cephalo-pelvic disproportion. Further research is warranted in order to assess if the use of customized growth charts specifically focused on the identification of fetal overgrowth may refine the prediction of the risk of obstetric intervention due to intrapartum dystocia.

Declaration of Competing Interest

The Authors state no financial disclosures nor conflict of interest related to the content of this work.

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References

- [1] American College of Obstetricians and Gynecologists (College), Society for Maternal-Fetal Medicine, Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. *Am J Obstet Gynecol* 2014;210 (March 3):179–93.
- [2] Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. *Obstet Gynecol* 2011;118 (July 1):29–38.
- [3] Hadlock FP, Harrist RB, Sharman RS, Deter RL, Park SK. Estimation of fetal weight with the use of head, body, and femur measurements- a prospective study. *Am J Obstet Gynecol* 1985;151:333–7.
- [4] Catalano PM, Tyzbir ED, Allen SR, McBean JH, McAuliffe TL. Evaluation of growth by estimation of neonatal body composition. *Obstet Gynecol* 1992;79:46–50.
- [5] Ak Sood, Yancey M, Richards D. Prediction of fetal macrosomia using humeral soft tissue thickness. *Obstet Gynecol* 1995;85:937.
- [6] Lee W, Deter R, Ebersole J, et al. Birth weight prediction by three-dimensional ultrasonography: fractional limb volume. *J Ultrasound Med* 2001;20:1283–92.
- [7] Lee W, Balasubramiam M, Deter RL, et al. Fractional limb volume- a soft tissue parameter of fetal body composition: validation, technical considerations and normal ranges during pregnancy. *Ultrasound Obstet Gynecol* 2009;33:427–40.
- [8] Favre R, Bader AM, Nidans G. Prospective study on fetal weight estimation using limb circumferences obtained by three-dimensional ultrasound. *Ultrasound Obstet Gynecol* 1995;6:140–4.
- [9] Hoopmann M, Abele H, Wagner N, et al. Performance of 36 different weight estimation formulae in fetuses with macrosomia. *Fetal Diagn Ther* 2010;27:204–13.
- [10] Bouvain M, Senat MV, Perrotin F, et al. Groupe de Recherche en Obstétrique et Gynécologie (GROG). Induction of labour versus expectant management for large-for-date fetuses: a randomised controlled trial. *Lancet* 2015;385(June 9987):2600–5.
- [11] Cunningham FG, Leveno KJ, Bloom SL, et al. *Williams obstetrics*. 24th edition New York: McGraw-Hill Education; 2014.
- [12] Ghi T, Dall'Asta A, Suprani A, et al. Correlation between subpubic arch angle and mode of delivery in large-for-gestational-age fetuses. *Fetal Diagn Ther* 2018;44(3):221–7.

- [13] Cha HH, Kim JY, Choi SJ, Oh SY, Roh CR, Kim JH. Can a customized standard for large for gestational age identify women at risk of operative delivery and shoulder dystocia? *J Perinat Med* 2012;40:483–8.
- [14] González-González NL, González-Dávila E, Cabrera F, et al. Application of customized birth weight curves in the assessment of perinatal outcomes in infants of diabetic mothers. *Fetal Diagn Ther* 2015;37:117–22.
- [15] Larkin JC, Speer PD, Simhan HN. A customized standard of large size for gestational age to predict intrapartum morbidity. *Am J Obstet Gynecol* 2011;204(499):e1–10.
- [16] Pasupathy D, McCowan LM, Poston L, Kenny LC, Dekker GA, North RA. Perinatal outcomes in large infants using customised birthweight centiles and conventional measures of high birthweight. *Paediatr Perinat Epidemiol* 2012;26:543–52.
- [17] Costantine MM, Mele L, Landon MB, et al. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, Bethesda, Maryland. Customized versus population approach for evaluation of fetal overgrowth. *Am J Perinatol* 2013;30(August 7):565–72.
- [18] Sjaarda LA, Albert PS, Mumford SL, Hinkle SN, Mendola P, Laughon SK. Customized large-for-gestational-age birthweight at term and the association with adverse perinatal outcomes. *Am J Obstet Gynecol* 2014;210(January 1):63 e1–63.e11.
- [19] Ghi T, Cariello L, Rizzo L, et al. Customized fetal growth charts for parents' characteristics, race, and parity by quantile regression analysis: a cross-sectional multicenter Italian study. *J Ultrasound Med* 2016;35(January 1):83–92.
- [20] Kiserud T, Piaggio G, Carroli G et al. The World Health Organization Fetal Growth Charts: A Multinational Longitudinal Study of Ultrasound Biometric Measurements and Estimated Fetal Weight. *PLoS Med.* 2017;14(Jan 1): e1002220. 10.1371/journal.pmed.1002220 eCollection 2017 Jan. Erratum in: *PLoS Med.* 2017 Mar 24;14 (3):e1002284. Erratum in: *PLoS Med.* 2017 Apr 20;14 (4):e1002301. PubMed PMID: 28118360; PubMed Central PMCID: PMC5261648.
- [21] World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Geneva: World Health Organization; 1999.
- [22] Italian Society on Ultrasound in Obstetrics and Gynecology (SIEOG). Guidelines. Available at. 2015. https://www.sigo.it/wp-content/uploads/2015/12/LineeGuidaSieog_2015.pdf.
- [23] Ghi T, Prefumo F, Fichera A, et al. Development of customized fetal growth charts in twins. *Am J Obstet Gynecol* 2017;216(5):514. doi:<http://dx.doi.org/10.1016/j.ajog.2016.12.176> e1–514.e17.
- [24] Bertino E, Spada E, Occhi L, et al. Neonatal anthropometric charts: the Italian neonatal study compared with other European studies. *J Pediatr Gastroenterol Nutr* 2010;51(September 3):353–61.
- [25] Ayres-de-Campos D, Spong CY, Chandraran E. FIGO intrapartum fetal monitoring expert consensus panel. FIGO consensus guidelines on intrapartum fetal monitoring: Cardiotocography. *Int J Gynaecol Obstet.* 2015;131(October 1):13–24.
- [26] Pritchard N, Lindquist A, Hiscock R, Diksha P, Walker SP, Permezel M. Customised growth charts in large-for-gestational-age infants and the association with emergency caesarean section rate. *Aust N Z J Obstet Gynaecol* 2019;59(June 3):380–6.
- [27] Von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of the Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1453–7.
- [28] Liselele HB, Boulvain M, Tshibangu KC, Meuris S. Maternal height and external pelvimetry to predict cephalopelvic disproportion in nulliparous African women: a cohort study. *BJOG* 2000;107(August 8):947–52.
- [29] Rozenholc AT, Ako SN, Leke RJ, Boulvain M. The diagnostic accuracy of external pelvimetry and maternal height to predict dystocia in nulliparous women: a study in Cameroon. *BJOG* 2007;114(May 5):630–5.
- [30] Connolly G, McKenna P. Maternal height and external pelvimetry to predict cephalo-pelvic disproportion in nulliparous African women. *BJOG* 2001;108(March 3):338.
- [31] Gardosi J, Francis A, Turner S, Williams M. Customized growth charts: rationale, validation and clinical benefits. *Am J Obstet Gynecol* 2018;218(February 2S):S609–18.
- [32] Figueras F, Gardosi J. Should we customize fetal growth standards? *Fetal Diagn Ther* 2009;25(3):297–303.
- [33] Gardosi J. Customized charts and their role in identifying pregnancies at risk because of fetal growth restriction. *J Obstet Gynaecol Can* 2014;36(May 5):408–15.
- [34] Gardosi J, Chang A, Kalyan B, Sahota D, Symonds EM. Customized antenatal growth charts. *Lancet* 1992;339:283–7.
- [35] Clausson B, Gardosi J, Francis A, Cnattingius S. Perinatal outcome in SGA births defined by customised versus population-based birthweight standards. *BJOG* 2001;108(August 8):830–4.
- [36] Odibo AO, Cahill AG, Odibo L, Roehl K, Macones GA. Prediction of intrauterine fetal death in small-for-gestational-age fetuses: impact of including ultrasound biometry in customized models. *Ultrasound Obstet Gynecol* 2012;39(March 3):288–92.
- [37] Anderson NH, Sadler LC, McKinlay CJD, McCowan LME. INTERGROWTH-21st vs customized birthweight standards for identification of perinatal mortality and morbidity. *Am J Obstet Gynecol* 2016;214(April 4):509 e1–509.e7.
- [38] Francis A, Hugh O, Gardosi J. Customized vs INTERGROWTH-21(st) standards for the assessment of birthweight and stillbirth risk at term. *Am J Obstet Gynecol* 2018;218(February 2S):S692–9.
- [39] Papageorgiou AT, Ohuma EO, Altman DG, et al. International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for fetal growth based on serial ultrasound measurements: the Fetal Growth Longitudinal Study of the INTERGROWTH-21st Project. *Lancet* 2014;384(September 9946):869–79. doi:[http://dx.doi.org/10.1016/S0140-6736\(14\)61490-2](http://dx.doi.org/10.1016/S0140-6736(14)61490-2) Erratum in: *Lancet.* 2014 Oct 4;384(9950):1264. PubMed PMID: 25209488.
- [40] Chiossi G, Pedroza C, Costantine MM, Truong VTT, Gargano G, Saade GR. Customized vs population-based growth charts to identify neonates at risk of adverse outcome: systematic review and Bayesian meta-analysis of observational studies. *Ultrasound Obstet Gynecol* 2017;50(Aug 2):156–66.
- [41] Rizzo G, Aiello E, Bosi C, D'Antonio F, Arduini D. Fetal head circumference and subpubic angle are independent risk factors for unplanned cesarean and operative delivery. *Acta Obstet Gynecol Scand* 2017;96(Aug 8):1006–11.
- [42] Malvasi A, Barbera A, Di Vagno G, et al. Asynclitism: a literature review of an often forgotten clinical condition. *J Matern Fetal Neonatal Med* 2015;28(November 16):1890–4.
- [43] Ghi T, Bellussi F, Pili G. Sonographic diagnosis of lateral asynclitism: a new subtype of fetal head malposition as a main determinant of early labor arrest. *Ultrasound Obstet Gynecol* 2015;45(Feb 2):229–31.
- [44] Ghi T, Dall'Asta A, Kiener A, Volpe N, Suprani A, Frusca T. Intrapartum diagnosis of posterior asynclitism using two-dimensional transperineal ultrasound. *Ultrasound Obstet Gynecol* 2017;49(June 6):803–4.
- [45] Dall'Asta A, Volpe N, Galli L, Frusca T, Ghi T. Intrapartum sonographic diagnosis of compound hand-cephalic presentation. *Ultraschall Med* 2017;38(October 5):558–9.
- [46] Wright D, Wright A, Smith E, Nicolaides KH. Impact of biometric measurement error on identification of small- and large-for-gestational-age fetuses. *Ultrasound Obstet Gynecol* 2020;55(2):170–6. doi:<http://dx.doi.org/10.1002/uog.21909>.
- [47] Khan N, Ciobanu A, Karampitsakos T, Akolekar R, Nicolaides KH. Prediction of large-for-gestational-age neonate by routine third-trimester ultrasound. *Ultrasound Obstet Gynecol* 2019;54(3):326–33. doi:<http://dx.doi.org/10.1002/uog.20377>.
- [48] Lipschuetz M, Cohen SM, Ein-Mor E, et al. A large head circumference is more strongly associated with unplanned cesarean or instrumental delivery and neonatal complications than high birthweight. *Am J Obstet Gynecol* 2015;213(6):833. doi:<http://dx.doi.org/10.1016/j.ajog.2015.07.045> e1–833.e12.
- [49] Mazzone E, Dall'Asta A, Kiener AJO, et al. Prediction of fetal macrosomia using two-dimensional and three-dimensional ultrasound. *Eur J Obstet Gynecol Reprod Biol* 2019;243:26–31. doi:<http://dx.doi.org/10.1016/j.ejogrb.2019.10.003>.