“INTERGROWTH21st vs customized fetal growth curves in the assessment of the neonatal nutritional status: a retrospective cohort study of gestational diabetes”

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Abstract
Background Gestational diabetes mellitus is associated with increased incidence of adverse perinatal outcomes including newborns large for gestational age, macrosomia, preeclampsia, polyhydramnios, stillbirth, and neonatal morbidity. Thus, fetal growth should be monitored by ultrasound to limit fetal overnutrition, and thereby, its clinical consequence, macrosomia. However, it is not clear which reference curve to use to define the limits of normality. Our aim is to determine which method, INTERGROWTH21st or customized curves, better identifies the nutritional status of newborns of diabetic mothers.

Methods This retrospective cohort study compared the risk of malnutrition in SGA newborns and the risk of overnutrition in LGA newborns using INTERGROWTH21st and customized birth weight references in gestational diabetes. Additionally, to determine the ability of both methods in the identification of neonatal malnutrition and overnutrition, we calculate sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios.

Results 231 pregnant women with GDM were included in the study. The rate of SGA identified by INTERGROWTH21st was 4.7% vs 10.7% identified by the customized curves. The rate of LGA identified by INTERGROWTH21st was 25.6% vs 13.2% identified by the customized method. Newborns identified as SGA by the customized method showed a higher risk of malnutrition than those identified as SGA by INTERGROWTH21st (RR 4.24 vs 2.5). LGA newborns according to the customized method also showed a higher risk of overnutrition than those classified as LGA according to INTERGROWTH21st (RR 5.26 vs 3.57). In addition, the positive predictive value of the customized method was superior to that of INTERGROWTH21st in the identification of malnutrition (32% vs 27.27%), severe malnutrition (22.73% vs 20%), overnutrition (51.61% vs 32.20%) and severe overnutrition (28.57% vs 14.89%).

Conclusions In pregnant women with GDM, the ability of customized fetal growth curves to identify the newborns with alterations in nutritional status exceeds that of INTERGROWTH21st.

Background
Gestational diabetes mellitus (GDM) is associated with increased incidence of adverse perinatal outcomes including newborns large for gestational age (LGA), macrosomia [1–4], preeclampsia [5],
polyhydramnios, stillbirth, and neonatal morbidity [6]. Newborns of mothers with GDM are heavier and have greater skinfold measures and adiposity than offspring of mothers without GDM. Later in life, children of diabetic mothers more frequently develop early overweight or obesity, type 2 diabetes, and metabolic syndrome. [7–9]

In pregnant women with GDM, fetal growth should be monitored by ultrasound to limit fetal overnutrition, and thereby, its clinical consequence, macrosomia. Prenatally, fetal overgrowth is suspected when the ultrasound estimated fetal weight (EFW) is abnormally elevated. An EFW higher than the 90th centile indicates an LGA fetus. This method is more accurate than that based only on the absolute value of the EFG (EFW greater than 4000 or 4500 g). By considering gestational age at the time of ultrasound, excessive fetal growth can be identified before the term [10]. Traditionally, fetal growth has been evaluated by comparing estimated fetal weight with population-based reference curves. Similarly, recent reports of the INTERGROWTH21st Project recommend using a single standard for fetal growth and birthweight [11–13]. Alternatively, a customized approach that uses a mathematical model of maternal anthropometric variables to predict the optimal weight at term of each fetus has gained strength recently [14,15]. This optimal weight at term can be combined with a fetal proportionality weight curve to calculate a customized curve for each mother in each pregnancy that can be used to predict birth weight and fetal growth. [16]

A few studies have compared INTERGROWTH21st and customized curves ability to identify fetuses at high risk of adverse perinatal outcomes, but not their ability to identify alterations in neonatal nutritional status. We hypothesized that, in pregnant women with GDM, customized curves identify the nutritional status of the newborn more accurately than INTERGROWTH21st. This study aims to determine which method, INTERGROWTH21 or customized curves, better identifies the nutritional status of newborns of diabetic mothers.

Methods
This study aims to determine which method, INTERGROWTH21 or customized curves, better identifies the nutritional status of newborns of diabetic mothers.
Design
This historical cohort study was conducted at the Department of Obstetrics and Gynecology of the University Hospital of Puerto Real (Cádiz/Spain). Medical records of all consecutive singleton births that occurred from January 2016 through March 2018 were retrieved from our database of information prospectively collected. Only pregnant women with GDM were included in the study. Congenital anomalies or stillborn babies were excluded from our study because of possible changes in fetal and birth weights. Gestational age was established based on the last menstruation and first ultrasound (usually at 11–12 weeks). In cases where the gestational age by ultrasound differed by ≥ 1 week, the last menstruation was corrected and stored in the information system.
Accepting an alpha risk of 0.05 and a beta risk of 0.2 (5% significance and 80% power) in a unilateral contrast, 39 subjects are required in the exposed group and 195 in the unexposed group, to detect a minimum relative risk of 3 and if the outcome rate of in the unexposed group is 0.1.
An exhaustive explanation of our customized method can be found in the study published by Fernández Alba et al [17].
To compare the two identification methods (INTERGROWTH21st and customized), two analyses were performed:
1. - Determination of the risk of alterations in the nutritional status of the newborn (malnutrition or overnutrition). To calculate the risk of neonatal malnutrition and severe neonatal malnutrition, the exposed group included newborns classified as small for gestational age (SGA) and the reference group included newborns classified as appropriate for gestational age (AGA). The same analysis was performed twice: one using INTERGROWTH21st as the curve of reference and another using our customized fetal growth curves as the reference. To calculate the risk of neonatal overnutrition and severe neonatal overnutrition, the exposed group included newborns classified as LGA and the reference group included newborns classified as AGA. Again, the analysis was performed twice: once using the INTERGROWTH reference method and the other using our customized curves.
2.- Determination of the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR-) of both methods for
identifying the nutritional status of the newborn.

Definitions

The diagnosis of GDM was established when at least two of the following four plasma glucose levels (measured at fasting, 1 hour, 2 hours, and 3 hours after a 100 g oral glucose tolerance test) were equal to or greater than 105 mg/ml, 190 mg/ml, 165 mg/ml and 145 mg/ml, respectively.

According to birth weight, newborns were classified as SGA (birthweight < 10th centile), AGA (birthweight between 10th and 90th centile), or LGA (birthweight > 90th centile) both by INTERGROWTH21st curves and by our customized curves.

The nutritional status of the newborn was evaluated using the ponderal index (PI) of Rohrer [18] adjusting by sex and gestational age. Proposed by Rohrer, the PI indicates how heavy a newborn is relative to its length [19–22]. The formula is as follows: PI = (weight in g × 100)/ (length in cm)^3. Because the PI relates to weight and length, it indicates body proportions, thus providing information about the nutritional status of newborn [23].

Neonatal malnutrition was defined as the PI < 10th centile; a PI between the 10th percentile and 90th centile was classified as normal; and a PI > 90th centile was classified as neonatal overnutrition. In addition, a PI < 3rd centile was classified as severe malnutrition and a PI > 97th centile was classified as severe overnutrition.

Statistical Analyses

Categorical data were summarized as counts and percentages. The distributions of continuous data were assessed using the Shapiro-Wilk test. Continuous data with a normal distribution were summarized as mean and standard deviation; by contrast, when the data showed a non-normal distribution, we used the median and the interquartile range as a measure of central tendency. The χ2-test was used to evaluate the differences in the frequency of SGA and LGA newborns according to each classification method.

The risks of malnutrition and severe malnutrition in newborns classified as SGA, by the INTERGROWTH21st and by our customized method, were calculated. Likewise, the risks of
overnutrition and severe overnutrition in newborns classified as LGA by these two methods were calculated. The results were expressed as relative risk (RR) and 95% confidence interval (95% CI). The, PPV, NPV, sensitivity, specificity, LR+ and LR- for the identification of malnutrition and overnutrition were calculated for newborns classified as SGA and LGA by both methods (INTERGROWTH21st and customized curves).

A p-value less than 0.05 was deemed statistically significant. All statistical analyses were performed using R statistical software v. 3.5.2 [24].

Results

This study recruited 234 pregnant women with GDM. In 3 cases the length of the newborn was missing, so 231 women remained in the study.

The maternal characteristics and perinatal outcomes are displayed in Table 1. The mean PI was 2.68 (SD: 0.26). The results of neonatal nutritional status are shown in Table 2. The incidence of malnourished newborns was 8.7%, and the incidence of neonatal overnutrition was 13.9%.

Table 3 shows the distribution of SGA, AGA and LGA newborns identified by each, INTERGROWTH21st and the customized, method. The rate of SGA newborns identified by INTERGROWTH21st was 4.7% versus 10.7% identified by our customized method. The rate of LGA newborns identified by INTERGROWTH21st was 25.6% vs 13.2% identified by the customized method (p<0.001).

Figure 1 shows the relative risk (RR) of malnutrition (PI < 10th centile) and severe malnutrition (PI < 3rd centile) in newborns classified as SGA and the RR of overnutrition (PI > 90th centile) and severe overnutrition (PI > 97th centile) in newborns classified as LGA by each of the methods, INTERGROWTH21st and customized. The risk of malnutrition in newborns classified as SGA by customized curves was 4.24 times that of newborns classified as AGA (RR 4.24, CI 95% 1.93—9.33). However, newborns classified as SGA using INTERGROWTH21st were not at significantly greater risk of malnutrition than those classified as AGA (RR 2.5, CI 95% 0.85—7.31). Likewise, newborns classified as SGA using the customized method had 8.58 times the risk of severe neonatal malnutrition of those classified as AGA (RR: 8.58, 95% CI 2.49—29.54). Although the incidence of severe malnutrition was greater in newborns classified as SGA using INTERGROWTH 21st than in
those classified as AGA, the risk was not significantly greater (RR 3.94, 95% CI 0.94—16.55) for SGA newborns.

In contrast, newborns classified as LGA, either both by INTERGROWTH21st or by the customized method, had a greater risk of overnutrition. However, the RR of overnutrition in newborns classified as LGA by the customized method was higher (RR: 5.26, 95% CI: 2.95—9.36) than that of newborns classified as LGA by INTERGROWTH21st (RR 3.57, 95% CI: 1.89—6.74).

LGA newborns also had a greater risk of severe neonatal overnutrition (PI > 97th centile). Again, the relative risk of severe neonatal overnutrition was greater when the customized method was used (RR: 21.28, 95% CI: 4.59—98.67) than when INTERGROWTH was used as the reference method (RR: 19.64, 95% CI: 2.48—155.59).

Table 4 shows the ability INTERGROWTH21st and our customized method to identify malnutrition in newborns classified as SGA. Both PPV and NPV were superior using the customized method than using INTERGROWTH21st. For identifying neonatal malnutrition, the PPV of the customized met was 32% (95% CI 11.71 - 52.29) versus 27.27% (95% CI 0 - 58.14) for INTERGROWTH21st; the NPV of the customized method was 92.45% (95% CI 88.03—96.87) versus 82.12% (95% CI 34.74—94.49) for INTERGROWTH21st.

The customized method also had greater ability to identify severe neonatal malnutrition, than did the INTERGROWTH21st method. For identifying severe neonatal malnutrition, the PPV of the customized method was 22.73% (95% CI 2.94—42.51) versus 20% (95% CI 0—49.79) for INTERGROWTH21st; the NPV of the customized method was 97.35 (CI95% 94.46—100) versus 94.93% (CI95% 90.90 vs 98.95) for INTERGROWTH21st.

For detecting both malnutrition and severe neonatal malnutrition, the customized method had an LR + superior to that of INTERGROWTH21st.

Table 5 shows sensitivity, specificity, predictive values and likelihood ratios of INTERGROWTH21st and customized methods for identification of overnutrition and severe overnutrition in newborns classified as LGA. The PPV of the customized method to identify both overnutrition and severe overnutrition was significantly higher than that of INTERGROWTH21st. For detecting overnutrition, the PPV of the
customized method was 51.61% (95% CI 32.41—70.82) versus 32.20% (95% CI 19.43—44.97) for INTERGROWTH21st. The between method difference was even greater for identification of severe overnutrition: the PPV of the customized method was 28.57% (95% CI 6.87—50.27) versus 14.89% (95% CI 3.65—26.14) for INTERGROWTH21st. However, NPVs of the two methods were very similar. The LR+ of the customized method was superior for identifying both overnutrition and severe overnutrition. For identifying overnutrition, the LR+ of the customized method was 5.40 (CI95% 2.98—9.78) versus 2.54 (CI95% 1.71—3.77) for INTERGROWTH21st. For identification of severe overnutrition the between method difference was greater: the LR+ of the customized method was 8.10 (CI95% 4.33—15.15) versus 3.74 (CI95% 2.57—5.45) for INTERGROWTH21st.

Discussion
Fetal weight estimation by ultrasound is important to the extent that truly reflects the fetal nutritional status. A fetus incorrectly classified as SGA or LGA will induce the clinician to intensify the monitoring of the pregnant woman and, in the specific case of the GDM, even to modify the diet or insulinize the pregnant woman. Therefore, we believe that the clinician should choose the curve that best identifies newborns with true alterations in nutritional status (malnutrition or overnutrition).
This study shows that in newborns of mothers with GDM, the rates of SGA and LGA differ by the reference curve used, INTERGROWTH21st or customized. The SGA rate using INTERGROWTH21st was 4.7%, significantly lower than 10.7% observed using customized curves. In contrast, the LGA rate using INTERGROWTH21st was 25.6%, compared to 13.2% using our customized curves as the reference. These SGA results were consistent with those recently published by Francis et al. [15] who reported overall SGA and LGA rates of 10.5% and 9.5%, respectively, using customized curves. However, our higher LGA rate (13.2% versus 9.5%) may due to the difference in the sample characteristic; Francis et al. included an unselected study population of pregnant women, whereas our study included only pregnant women with GDM, and they are more likely to birth LGA newborns.
Using INTERGROWTH21st Francis et al. observed an overall SGA rate, 4.4%, very similar to the 4.7% rate of our sample. However, using INTERGROWTH21st, Francis et al observed a lower LGA rate, 20.6%, than the 25.6% found by us, perhaps due to our inclusion of exclusively mothers with GDM,
whereas Francis et al. evaluated an unselected sample.

Similarly, Anderson et al. [25], reported a significantly lower SGA rates using INTERGROWTH21st versus customized curves (4.5% vs 11.6%); LGA rates were not assessed in this general obstetric population.

In addition, we found that the SGA and LGA classifications by each method (customized vs INTERGROWTH21st) reflect differences in their ability to identify true alterations in the neonatal nutritional status, as indicated by the ponderal index. We found that in newborns of mothers with GDM, the RR, 4.24, of malnutrition (PI <10th percentile) in newborns classified as SGA by customized curves was higher, than that of newborns classified as SGA by INTERGROWTH21st, RR = 2.5.

Likewise, the accuracy of the customized curves for identification of malnutrition was greater than that of INTERGROWTH21st, LR + of 3.86 vs 2.74, respectively. That is, using customized curves, it is 3.86 times more likely that a malnourished newborn is classified as SGA than a normally nourished newborn is classified as SGA. The customized curves were also more accurate than INTERGROWTH21st for identifying severe malnutrition, LR + of 5.36 versus 3.86, respectively.

In a previous study by our team [17], carried out in an unselected population, the customized method was superior to the population-based for the identification of newborns with malnutrition. This superiority of the customized method was more evident in the highest scales of maternal weight and height.

Owen et al. [26] found a similar relationship between customized birth weight percentiles and neonatal malnutrition, but concluded that, in a low-risk population, the customized curves are only moderately useful in the identification of neonates with a low PI, with a positive likelihood ratio of 4.3 (95% CI: 2.5–7.1). Agarwal et al [27] also found that the PI at birth was lower in newborns classified as SGA by customized curves than in SGA according to population curves.

Similarly, the RR of overnutrition (PI> 90th centile) associated with LGA classification by customized curves, RR 5.26, was greater than in the newborns classified as LGA by INTERGROWTH21st, RR 3.57). Further, our analysis of the accuracy of each method for identification of overnutrition revealed that the customized method had a greater LR+, 5.40, than the LR+, 2.54, using INTERGROWTH21st.
Hence, using customized curves, it is 5.40 times more likely that an over nourished newborn will be classified as LGA than a normally nourished newborn will be classified as LGA. For identification of severe overnutrition, we observed an even greater between method difference: the LR+ of the customized method was much greater, 8.10, than that of INTERGROWTH21st, 3.74. This indicates that using customized curves, it is 8.10 times more likely that a severely over nourished newborn is classified as LGA than a normally nourished newborn is classified as LGA. Given that in GDM it is critical to identify fetal overnutrition, we consider of special relevance the differences found in the PPV of both methods to identify overnutrition. Using our customized curves, the probability that a fetus classified as LGA suffers from overnutrition is 51.61% while using INTERGROWTH21st the probability drops to 32.20%. In the same way, using our customized curves, a fetus classified as LGA is twice as likely to be severely over nourished as if we were using INTERGROWTH21st (28.57% vs. 14.89%). Estos resultados son coherentes con los hallados por Gonzalez et al [28]

The relatively small sample lead to our primary limitations, including occasional RRs with overlapping or wide confidence intervals, which hampered their interpretation. However, the relative risks were usually large enough to be taken clinically relevant. In addition, selection and information biases could affect the estimated of the performance of the two reference curves. We believe that our results can be extrapolated to other populations of pregnant women with adequate monitoring because obstetricians, endocrinologists, family doctors and primary care midwives monitored the pregnant woman with GDM using criteria for diagnosis, follow-up and treatment established by the Spanish Society of Gynecology and Obstetrics.

Conclusions
In pregnant women with GDM, the ability of customized fetal growth curves to identify the newborns with alterations in nutritional status exceeds that of INTERGROWTH21st. In our opinion, the greater capacity of the customized curves to identify newborns with overnutrition may have important implication for monitoring pregnant women with GDM because intrauterine identification of overnutrition may indicate poor maternal metabolic control and the need for extreme dietary care or, even, insulin treatment. However, the results must be interpreted with caution because future studies
with a larger sample size are needed to increase the reliability of these findings.

Abbreviations
GDM: Gestational diabetes mellitus
LGA: Large for gestational age
EFW: Estimated fetal weight
SGA: Small for gestational age
AGA: Adequate for gestational age
PPV: Positive predictive value
NPV: Negative predictive value
LR+: Positive likelihood ratio
LR-: Negative likelihood ratio
PI: Ponderal index
RR: Relative risk
CI: Confidence interval

Declarations

Ethics approval and consent to participate
The present study was approved by the Comité Coordinador de Ética de la Investigación de Andalucía, Consejería de Salud, Junta de Andalucía (SPAIN) with the protocol number 0532-N-17. Due to the retrospective nature of the study, no informed consent was required.

Consent for publication
Not applicable

Availability of data and materials
The datasets generated and/or analysed during the current study are available in ONEDRIVE with this link https://1drv.ms/u/s!AnSC–9_Msj6-g4gXADvN6r9fwAfQ8w?e=YlUY3e

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
JJFA, LJMC and JASB contributed the idea of the study and the statistical analysis. ESP, RMC, AVS, CGM
and MCL contributed in participants selection and data collection in the field. All the authors contributed to writing of the manuscript and all read and approved the final manuscript.

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Tables
Due to technical limitations, tables are only available as a download in the supplemental files section

Figures
Figure 1

Risk of malnutrition and severe malnutrition in newborns classified as SGA and risk of overnutrition and severe overnutrition in newborns classified as LGA by the INTERGROWTH21st and customized methods. Forest plots showing RRs and 95% confidence interval

Supplementary Files

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