Development of Reference Percentile Growth Curves for Placental Parameters Using Advanced Statistical Models

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Abstract. There has been a growing interest in assessing placental biometric parameters and their relationship with obstetric outcomes, highlighting their utility in reflecting changes in fetal development and long-term health. However, research focus on fetal development over the placental has caused many gaps in our knowledge about the biological role of placental abnormalities. This study aims to establish reference percentile curves for placental and fetal biometric parameters using data from Portuguese parturients. Nonlinear regression models, including Generalized Additive Models for Location, Scale, and Shape (GAMLSS) and Lambda-Mu-Sigma (LMS) methods, were chosen due to their flexibility in handling diverse statistical distributions. The application of the GAMLSS method with Box-Cox t (BCT) distribution and P-splines to Diameter 1, Diameter 2, Placental Volume, and FW/PW Ratio parameters, and LMS Box-Cox t (LMST) method to Placental Thickness, Placental Weight, and Fetal Weight parameters, results in representative percentile growth curves. This study successfully developed placental growth curves using nonlinear regression models, providing valuable information on placental development and its clinical implications in obstetrics. The reference growth curves enhance the monitoring of maternal-fetal health and can guide clinical decisions, especially in addressing contemporary challenges, such as low birth rates and increasing maternal age.

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1 Introduction

In the initial phases of fetal development, a complex interaction between genes and environment is found to be partly responsible for shaping human behaviour and susceptibility to diseases [6]. It is imperative to acknowledge the role of early detection of growth anomalies, especially those related to the functioning of the placenta, to minimize the risks associated with fetal disorders and illnesses in adulthood.

Recently, a growing focus has been placed on using different indices to examine fetal development, particularly in evaluating the biometric parameters of the placenta and their relationship to obstetric outcomes [21,26,28]. Research findings imply that some pregnancy complications, such as decreased fetal activity, intrauterine size deficits, and later individual health problems, are linked with the structure of the placenta [19,24,48].

When properly studied, the parameters of the placenta can be useful in narrowing down cases of perinatal mortality and neonatal diseases. There is a growing demand for pathological placental studies, and their understanding is crucial for expanding the use of placental examinations and measures [3,22]. Parameters like placental diameter (D1—larger or D2—smaller), placental thickness (PT), placental weight (PW), placental volume ($D1 \times D2 \times PT$) (PV), fetal weight (FW) and FW/PW ratio (R-FW) are acknowledged as vital in evaluating placental function and fetal growth [18,21,26]. Consequently, advancements in understanding these parameters in relation to gestational age (GA) can significantly contribute to the early recognition of fetal disorders.

Research focus on fetal development over the placental has caused many gaps in our knowledge about the biological role of placental abnormalities during childbirth and the first weeks after birth [26]. This emphasizes the importance of increased attention to studies and tools that are tailored to differentiate challenging placental characteristics. Growth curve models specifically stand out for this purpose, as they are valuable for monitoring variations in placental weight and diameter throughout GA. While birth weight percentile curves are extensively used to monitor fetal growth and classify the risk of certain fetal conditions [20], studies focusing on percentile curves for placental data, such as, D1, D2, PT, PW, PV and R-FW, are scarce. Existing studies on fetal and placental percentile curves primarily refer to GA above 24 weeks, and some of this information may be outdated. Therefore, it is imperative to study and update information related to these growth curves. Despite the need for additional evidence, percentile curves remain relevant for monitoring fetal growth, and optimizing their understanding can enable early intervention in adverse fetal conditions.

The use of percentile growth curves is important to determine and measure placental characteristics. Nonlinear regression models tend to be the preferred choice in this analysis because they usually outperform linear models. Several

researchers investigated the nonlinear model's ability to accurately describe different growth patterns [8,21,27]. In our study, we propose employing semiparametric regression models under the framework of Generalized Additive Models for Location, Scale, and Shape (GAMLSS) [33], as well as Lambda-Mu-Sigma (LMS) models [11,12,32,34], to model various parameters such as D1, D2, PT, PW, PV, FW and R-FW.

This study makes a substantial contribution to understanding placental metrics and growth curve modelling. It underlines the vital role of placental biometric data in predicting the outcomes of pregnancy and fetus health. Besides, it presents the applicability of GAMLSS framework for accurate and flexible estimation of percentile growth curves based on placental metrics. The study results highlight the reliability of these curves, especially at the distribution tails, which are particularly important for clinical assessments.

The primary aim of this study is to improve early detection of fetal growth deviations by developing accurate placental growth reference curves. Thus, diverse growth curve models were implemented, and their performance was compared to identify the model that best represents each parameter under study. These models hold the potential to be useful in various ways, promoting advances in placental and fetal monitoring, and thereby enhancing the evaluation of placental function and perinatal care. Consequently, this research may offer psychosocial relief to families and contribute to an increase in perinatal success and birth rates.

This paper is divided into five sections. Section 2 describes the dataset and explains the methods used to model the growth curves. Section 3 presents the results, while Sect. 4 discusses their significance. Finally, Sect. 5 summarizes the findings and suggests future research directions.

2 Material and Methods

2.1 Dataset

In this study, growth curves for various placental parameters were modelled as a function of gestational age (GA) for the Portuguese population. The dataset used to develop and test the generated models partly overlapped with two previous studies [21,26]. It began with an analysis of 7321 placental samples that were meticulously processed at the Embryonic-Fetal Pathology Laboratory, located at Centro de Genética Clínica (CGC), Unilabs, Porto, Portugal, and were preprocessed (details can be found in [26]). The information collected from the placental pathological reports spanned a four-year period, from January 1, 2014, to December 31, 2017. The reports encompassed a broad range of GA, ranging from 12 to 41 weeks.

For this study, the dataset was extended, incorporating new cases that adhered to the criteria initially outlined by [26]. The final dataset under study, post-preprocessing, comprised a set of $n = 2092$ placental samples. The variables modelled included the following placental parameters: D1, D2, PT, PW, PV, FW, and R-FW.

2.2 Modelling Strategies for Placental Growth Curves

The development of growth curves requires a selection of methods that consider the characteristics of the dataset under analysis and its future applications. The methodology for implementing the curves was divided into several interconnected sections, outlining the process from method review to fit quality assessment. In a previous study by the authors [21], this methodology was analyzed in detail for modelling a placental parameter, D2. Therefore, this study should be referred to for additional information.

All analyses and the development of growth curves were conducted in R using the `gamlss` and `ggplot2`, and `dplyr` packages, which provided a flexible framework for statistical modelling, visualization, and data manipulation.

Figure 1 provides a summary of the methodology used in developing the growth curves. Initially, a critical review of existing methods for modelling growth curves was conducted. Subsequently, based on this review and considering the criteria outlined in Subsect. 2.2, several methods were selected: GAMLSS, LMS, Lambda-Mu-Sigma Box-Cox t (LMST), and Lambda-Mu-Sigma Box-Cox-Power-Exponential (LMSP). Each of these methods offers unique approaches to modelling growth curves.

Within each method, specific distributions that best suit the context of this study were explored. This includes the Box-Cox Cole-Green (BCCG), Box-Cox t (BCT), Box-Cox Power Exponential (BCPE), and Johnson's SU (JSU) distributions. These distributions play a fundamental role in representing the data characteristics. Four smoothing techniques were selected: P-splines, Cubic Splines, Neural Networks, and Loess. Each of these techniques is designed to capture different growth patterns. Finally, several goodness-of-fit criteria were selected, including the Coefficient of Determination (R^2), Mean Square Error (MSE), Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), Z-Statistics, Worm plots, and Residual plots.

This methodology was then applied to various models, aiming to identify the most appropriate model for each of the placental parameters under study, namely D1, D2, PT, PW, PV, FW, and R-FW. It is noteworthy that it followed a specific order of procedures. Initially, various smoothing functions were evaluated in a GAMLSS model without imposing a specific distribution for the model. These smoothing functions are known for their flexibility in fitting curves without the need to predefine a specific form for the underlying function [14]. The purpose of this approach lies in simplifying the modelling process. Simultaneously incorporating smoothing functions and distributions would significantly increase the complexity of the modelling process. Subsequently, various distributions were tested in combination with the chosen smoothing function, using different methods. Finally, the fit quality of each model was evaluated.

Criteria for Method Selection. In this study, several criteria were considered to guide the selection of methods for developing the percentile growth curves. Accuracy in estimating extreme percentiles was prioritized due to data scarcity in this region, necessitating methods that rely on an underlying distribution.

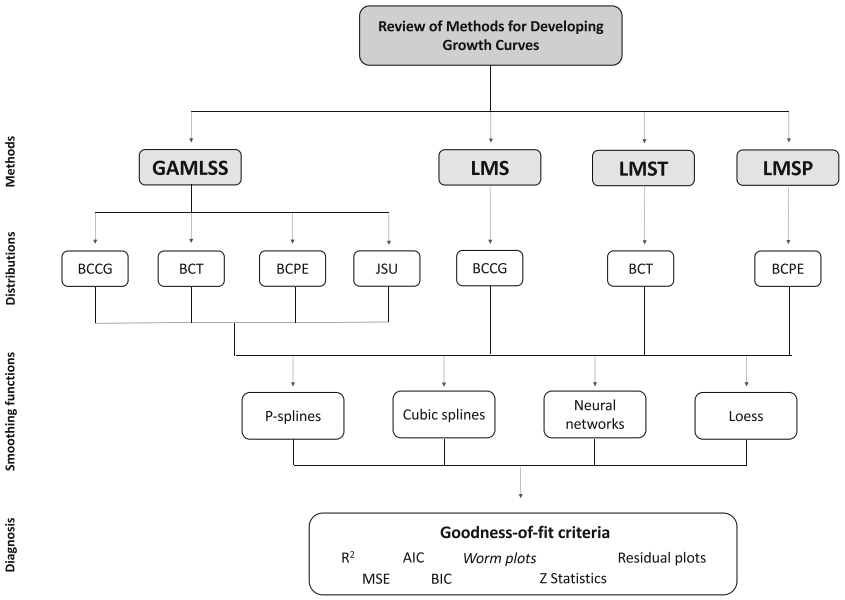

Fig. 1. Workflow illustrating the methodology for developing placental growth curves. Steps include: (1) Reviewing growth curve methods, (2) Selecting methods, (3) Choosing distributions, (4) Applying smoothing functions, and (5) Evaluating Goodness-of-fit criteria. Models were applied to placental parameters D1, D2, PT, PW, PV, FW and R-FW.

Preventing percentile curve crossing was crucial, requiring simultaneous calculation to ensure interpretable percentiles. Facilitating retrotransformations was essential for the direct calculation of percentiles and z-scores, and handling kurtosis alongside skewness was important to preserve the integrity of adjusted percentiles.

In addition to these main criteria, secondary criteria were also considered. Compatibility with diagnostic tools ensures reliable results by evaluating fit quality. Computational efficiency is important for efficient curve construction when comparing methods. Applicability flexibility allows the method to be applied to various measurements, making growth curves applicable in diverse contexts.

GAMLSS, LMS and Its Extensions LMST and LMSP. Introduced by Rigby and Stasinopoulos [33], along with contributions from Akantziliotou *et al.* [2], GAMLSS are semi-parametric regression models. They exhibit parametric characteristics, as they require an assumption of a parametric distribution for the response variable. However, they are considered semi-parametric because the modelling of distribution parameters, in relation to explanatory variables, can incorporate non-parametric smoothing functions [40]. They allow the use of a wide range of distributions, including continuous and discrete distributions with

significant skewness and kurtosis [45]. What distinguishes GAMLSS is its ability to model not only the mean (or location) but also other critical distribution parameters, such as scale, skewness, and kurtosis [41].

For the statistical model of GAMLSS, let's assume that the response variable Y follows a four-parameter distribution $Y \sim D(\boldsymbol{\theta})$ with $\boldsymbol{\theta} = (\mu, \sigma, \nu, \tau)$ [40]. Where μ and σ are generally referred to as location and scale parameters, while ν and τ are considered shape parameters, e.g. skewness and kurtosis. The Eq. 1 specifies $g_k(\boldsymbol{\theta}_k)$ as the linear predictor $\boldsymbol{\eta}_k$, which combines fixed effects $\mathbf{X}_k\boldsymbol{\beta}_k$ and potentially non-linear and random effects $\sum_{j=1}^{J_k} \mathbf{Z}_{jk}\boldsymbol{\gamma}_{jk}$. Here, $\mathbf{X}_k$ represents the design matrix for fixed effects, $\boldsymbol{\beta}_k$ is the parameter vector, $\mathbf{Z}_{jk}$ is the design matrix for random effects, and $\boldsymbol{\gamma}_{jk}$ are the corresponding random effect parameters [40].

$$g_k(\boldsymbol{\theta}_k) = \boldsymbol{\eta}_k = \mathbf{X}_k\boldsymbol{\beta}_k + \sum_{j=1}^{J_k} \mathbf{Z}_{jk}\boldsymbol{\gamma}_{jk} \quad \text{for } k = 1, 2, 3, 4 \tag{1}$$

Estimation in GAMLSS is typically performed by maximizing a penalized likelihood function. There are two fundamental algorithms for this purpose, however, during this study, RS was exclusively used due to its effectiveness in treating a wide range of distribution families and its computational efficiency. The Rigby and Stasinopoulos algorithm (RS) is an approach derived from the algorithm used in fitting Mean and Dispersion Additive Models (MADAM) models by [30,31].

The LMS method, developed by Cole [13] and subsequently refined by Cole and Green [12], is a tool for modelling a response variable Y against a single explanatory variable x (e.g., age) [42]. It supports specific distributional assumptions for Y, enabling simultaneous estimation of multiple percentiles without crossings. In GAMLSS, the LMS method integrates assuming Y follows the BCCG distribution for data exhibiting skewness with $Y > 0$. Rigby and Stasinopoulos [32,34] extended the LMS method by introducing the BCT and BCPE distributions for Y, facilitating percentile estimation methods LMST and LMSP.

The final GAMLSS and LMST models for all studied placental parameters utilized the BCT distribution and P-splines as the smoothing function. Further information on this distribution and smoothing function can be found in the authors' previous study [21].

Goodness-of-Fit Criteria. The goodness-of-fit evaluation is crucial in statistical analysis, ensuring the reliability of estimates and the accuracy of the developed reference growth curves. This study used the following quantitative criteria and graphical tools to evaluate the models:

- **Determination Coefficient** (R^2): quantifies how well a model fits data, ranging from 0 to 1, with higher values indicating better fit [10,47].

- **Mean Square Error (MSE):** measures predictive model accuracy, with lower values indicating better fit by minimizing squared differences between predicted and actual values [10,37].
- **Akaike's Information Criterion (AIC):** is a fundamental tool for model selection, balancing model complexity with fit quality based on a mathematical framework that includes a penalty for the number of parameters [1,7].
- **Schwarz Bayesian Information Criterion (BIC):** similar to AIC but penalizing more complex models, aids in selecting parsimonious models [25, 38].
- **Worm plot:** visually assesses model fit by plotting standardized residuals against expected values, indicating the adequacy of the model fit based on deviations from a standard normal distribution [9,42].
- **Z-statistics:** assess residual normality across age groups, crucial in percentile estimation [36,42].
- **Residual plots:** assess model fit quality and identify potential model assumption violations [42]. In this study, four key residual plots were analyzed, including quantile residuals against fitted values of the parameter μ, against specified indices or covariates, kernel density estimation of residuals, and Normal Q-Q plot.

3 Results

3.1 Exploratory Analysis

Exploratory analysis plays a fundamental role in understanding the data underlying the development of growth curves for placental parameters as a function of GA.

Table 1 presents descriptive statistics such as mean, standard deviation (SD), minimum (Min), maximum (Max), median, skewness, and kurtosis of the placental parameters under study. These statistics offer a comprehensive understanding

Table 1. Descriptive statistics of D1, D2, PT, PW, PV, FW, and R-FW. The table includes the mean, standard deviation (SD), minimum (Min), maximum (Max), median, skewness, and kurtosis for each placental parameter in the study.

Placental parameter	Mean	SD	Min	Max	Median	Skewness	Kurtosis
Placental Diameter 1	13.39	4.90	2.00	32.00	13.00	0.50	3.23
Placental Diameter 2	11.21	4.47	1.50	30.00	11.00	0.29	2.87
Placental Thickness	2.10	0.70	0.30	5.00	2.00	0.71	4.02
Placental Weight	229.77	158.08	6.00	995.00	190.00	0.81	3.25
Placental Volume	387.80	327.15	4.80	2345.25	305.70	1.45	6.05
Fetal Weight	1229.58	1152.07	5.70	4880.00	736.50	0.74	2.34
Ratio-FW	4.24	2.41	0.21	11.51	4.12	0.18	2.03

of trends, variability, and distributional characteristics, demonstrating the complexities of placental development and its implications for fetal health.

The mean values for Diameter 1 and Diameter 2 were 13.39 cm (SD = 4.90 cm, range = 2.00–32.00 cm) and 11.21 cm (SD = 4.47 cm, range = 1.50–30.00 cm), respectively. Both diameters exhibited a slight rightward skew (Skewness = 0.50 for D1 and 0.29 for D2) and had kurtosis values suggestive of a leptokurtic distribution (Kurtosis = 3.23 for D1 and 2.87 for D2). Placental thickness had a mean of 2.10 cm (SD = 0.70 cm, range = 0.30–5.00 cm) and displayed a more pronounced skewness (0.71) and high kurtosis (4.02), indicating a distribution with heavier tails than a normal distribution. Placental weight had a mean of 229.77 g (SD = 158.08 g, range = 6.00–995.00 g) and exhibited a skewness of 0.81 and a kurtosis of 3.25. The volume demonstrated the most significant variability and skewness (Skewness = 1.45, Kurtosis = 6.05) with a mean of 387.80 cm^3 (SD = 327.15 cm^3, range = 4.80–2345.25 cm^3), suggesting a highly skewed distribution with a long right tail. Fetal weight showed a broader distribution with a mean of 1229.58 g (SD = 1152.07 g, range = 5.70–4880.00 g), a skewness of 0.74, and a kurtosis of 2.34. The Ratio-FW had a mean of 4.24 (SD = 2.41, range = 0.21–11.51), indicating the least skewness (0.18) and the lowest kurtosis (2.03) among all variables, which suggests a distribution that is closest to normal.

3.2 Significance Tests Between Genders

Statistical analysis was performed using the Student's t-test (respecting the criterion of normality and/or the conditions of applicability of the Central Limit Theorem) with a 5% significance level to identify statistically significant differences between the means of placental parameters D1, D2, PT, PW, and FW for female and male fetuses at each GA. See Fig. 2 for a visual representation of the mean values and their 95% confidence intervals.

Significant differences were found for certain placental parameters at specific GAs. For example, D1 showed significance at week 39 (p-value = 0.04), while D2 at weeks 12 (p-value = 0.009), 14 (p-value = 0.03), and 39 (p-value = 0.006). PT had significant differences at weeks 14 (p-value = 0.02), 20 (p-value = 0.04), and 40 (p-value = 0.02), while FW showed significance at weeks 16 (p-value = 0.009) and 40 (p-value = 0.002). It is noteworthy that PW did not present significant differences at any GA.

3.3 Growth Curves

In this study, the relationship between various placental parameters such as D1, D2, PT, PW, PV, FW and R-FW with GA was analysed to produce reference percentile growth curves at specific percentiles ($3^{rd}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 97^{th}$).

Due to the extensive analysis of evaluation criteria, which includes a large number of figures and tables, it was decided to include only the metrics values for the final model of each placental parameter and diagnostic graphical analyses only for the PV in this document, as the diagnostic graphical analysis for the

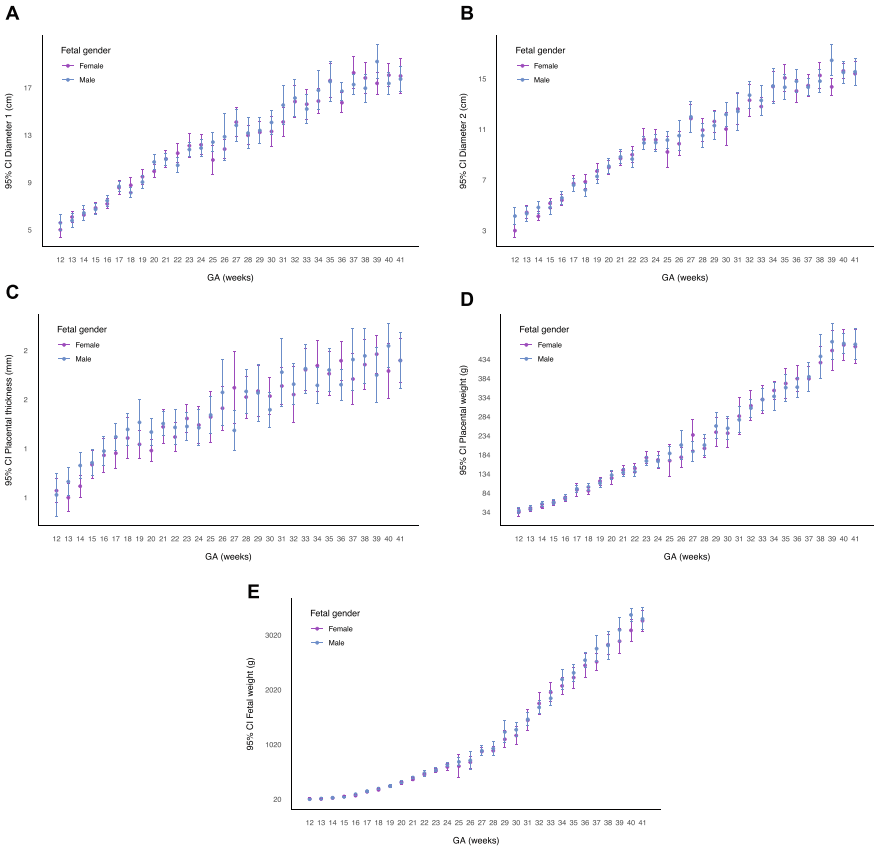

Fig. 2. Mean values and 95% confidence intervals for D1, D2, PT, PW, and FW across gestational age (GA) for female and male fetuses. Statistical significance was evaluated using Student's t-test ($\alpha = 0.05$).

final models of the remaining placental parameters is similar. The other figures and tables, covering all analysed quality criteria, are available in the GitHub [1] repository.

The final models for each placental parameter were selected by choosing the model that achieved the highest R^2 and the lowest MSE, AIC, and BIC among all models evaluated, as summarized in Table 2.

For D1, the model with the best performance was GAMLSS with the BCT distribution, with a R^2 value of 0.755. This indicates a good fit to the data, with

[1] https://github.com/daniellalemos/Growth_curves.

minimal deviation between predicted and observed values, as reflected in the MSE of 4.593. Additionally, the AIC and BIC values of 9439 and 9529, respectively, suggest a good fit for the model. Similarly, for D2, GAMLSS with the BCT distribution stood out as the optimal model, with a R^2 value of 0.765 and a relatively low MSE of 4.398. The AIC and BIC values of 9029 and 9142, respectively, further support the adequacy of this model in capturing the variability in D2 measurements over GA. For PT, PW, and FW, the LMST model was identified as the best fit. Despite a lower R^2 value of 0.390 for PT, the LMST model showed satisfactory performance, especially considering the complex nature of the data. For PW, a good fit was observed with a R^2 value of 0.852 and AIC and BIC values of 22281 and 22403, respectively. For FW, a R^2 value of 0.962 and AIC and BIC values of 26679 and 26874 were obtained. Finally, for PV and R-FW, GAMLSS with the BCT distribution was again identified as the best fit, with R^2 values of 0.824 and 0.845, respectively. R-FW showed a relatively low MSE value of 2.621. The AIC values of 25112 and 5394 and the BIC values of 25220 and 5529, respectively, further support the adequacy of these models in capturing variability over GA.

Table 2. Summary of model performance metrics (R^2, MSE, AIC, and BIC) for the final models developed.

Placental parameter - Model	**R^2**	**MSE**	**AIC**	**BIC**
Placental Diameter 1 - GAMLSS	0.755	4.593	9439	9529
Placental Diameter 2 - GAMLSS	0.765	4.398	9029	9142
Placental Thickness - LMST	0.390	1.552	3210	3288
Placental Weight - LMST	0.852	10.890	22281	22403
Placental Volume - GAMLSS	0.824	12.262	25112	25220
Fetal weight - LMST	0.962	13.110	26679	26874
Ratio-FW - GAMLSS	0.845	2.621	5394	5529

In addition to these metrics, an evaluation of the fit quality was also performed using graphical diagnostic criteria, such as Z-statistics, worm plots, and residual plots. Figure 3 shows these metrics for the final model of the PV. The remaining placental parameters exhibited very similar metrics. Looking at the worm plot, a good fit to the data is notable, as the points and the fitting line are very close to the horizontal reference line, and more than 95% of these points are within the confidence intervals. Z-statistics also indicated a good fit, with no $|Z| > 2$ values.

Regarding the residuals, they indicate acceptable behaviour in the graph concerning the indices, but in the plot relative to the fitted values, there is a pattern of vertical lines, indicating that the variability of the errors is not constant along the range of predicted values. Additionally, an approximation to normality was observed, as evidenced by the two lower residual plots.

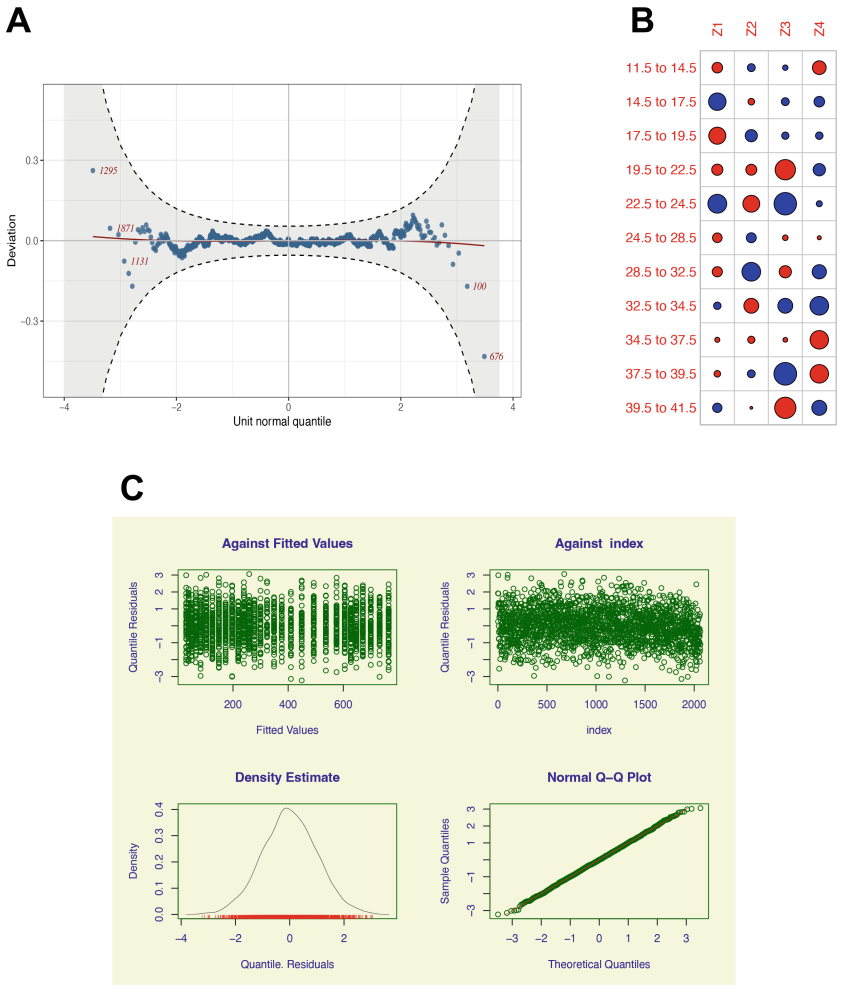

Fig. 3. Goodness-of-fit criteria (worm plot, Z-statistics, and residual plots) for the Placental volume using the GAMLSS model with P-splines and the BCT distribution.

The growth percentile curves for the final models of each placental parameter are represented in Fig. 4. It is evident that these curves accurately capture the data behaviour. As a final diagnostic of the models, the percentages of the sample located at or below each fitted curve are presented in Table 3. The close agreement between the nominal and sample percentiles for the various models suggests a good fit of the percentile curves.

Table 3. Nominal percentiles (%) of the sample located at or below each fitted curve for the placental parameters D1, D2, PT, PW, PV, FW and R-FW.

Nominal percentile	**3**	**10**	**25**	**50**	**75**	**90**	**97**
Placental Diameter 1	3.05	10.37	25.05	50.29	75.63	90.02	96.75
Placental Diameter 2	3.00	9.21	24.37	49.08	74.61	90.07	96.56
Placental Thickness	3.59	8.67	27.33	49.32	74.37	89.83	96.27
Placental Weight	3.44	10.37	24.32	49.32	75.39	90.55	97.43
Placental Volume	3.30	9.69	24.81	49.76	75.15	90.12	96.95
Fetal weight	3.30	11.39	25.44	48.35	74.81	90.65	97.63
Ratio-FW	2.91	10.13	24.32	50.48	74.81	89.87	96.56

4 Discussion

Throughout the years, researchers have developed percentile growth curves for FW, offering important information for healthcare professionals and parents about fetal and neonatal growth patterns [5,17]. The current study's findings show the feasibility of developing similar percentile growth curves for placental metrics such as D1, D2, PT, PW, PV, and R-FW. These charts can be beneficial for a more detailed examination of fetal health because, as discussed in the literature, there is a correlation between placental morphology and size with pregnancy complications and subsequent health of the child [23,39].

The exploratory data analysis, presented in Sect. 3.1, has provided the basis for developing these percentile curves. There was a progressive growth in all placental parameters, which suggests a positive correlation between them and GA. The skewness and kurtosis values indicate that most placental parameters have distributions that deviate from normality, with a tendency to have a rightward skew and leptokurtic characteristics, particularly in PV and FW. This implies that while most of the placentas and fetuses are within their expected sizes, some extreme values could be attributed to certain health risks or developmental abnormalities. There was also significant variability for FW, indicated by the high SD values, which is expected as pregnancy progresses and there are greater differences between fetuses and placentas. The observed results for all measured placental parameters are consistent with previous research emphasizing the continuous growth of the placenta and fetus during pregnancy [15,44]. The data's positive kurtosis suggests the necessity for techniques capable of handling this issue, like the implemented GAMLSS method, to prevent skewed adjusted percentiles [8].

Since fetal gender is acknowledged to be related to birth weight, it may be important to have separate curves for female and male genders. While some studies indicate no significant gender differences in placental weight [4,26,43], some differences were found in a small percentage (6.2%) of cases. This scenario implies that, in general, percentile curves for placental parameters can be applied

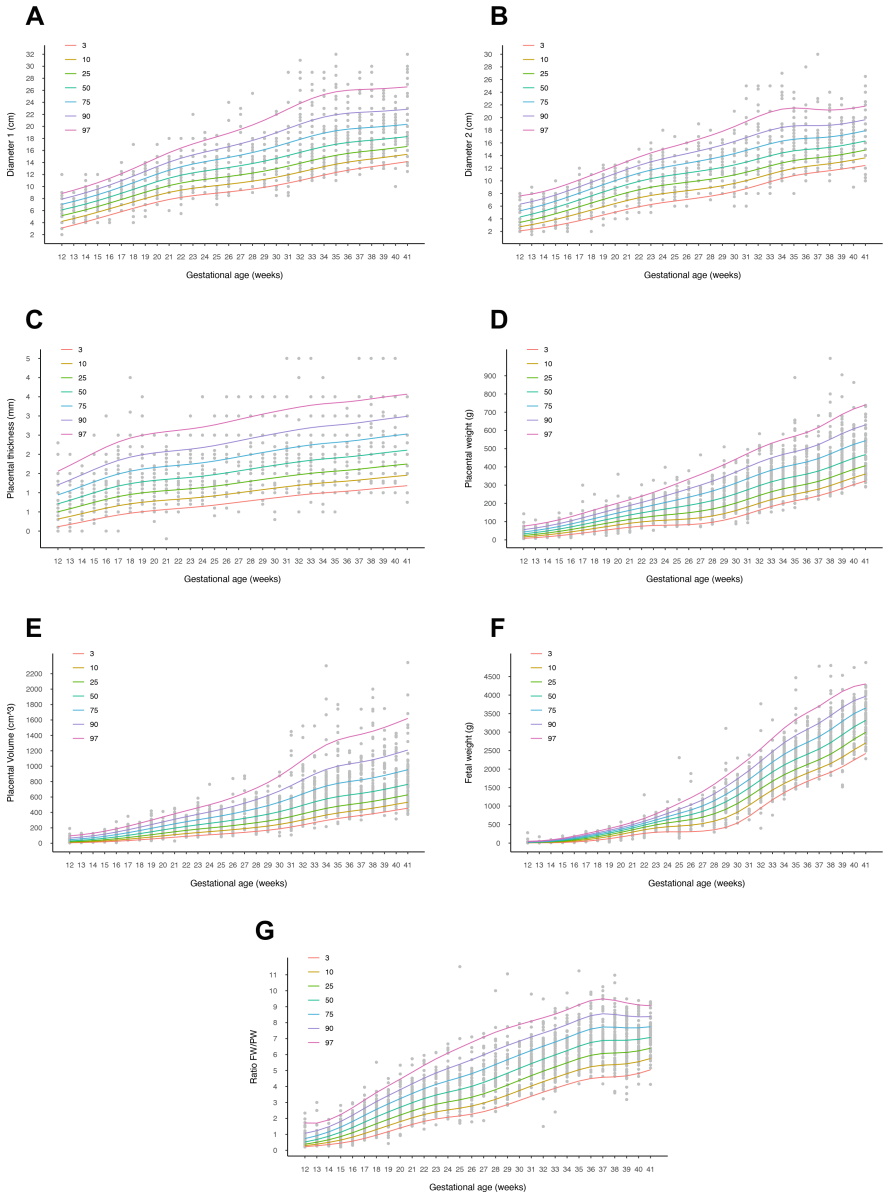

Fig. 4. Observed Diameter 1 (A), Diameter 2 (B), Placental thickness (C), Placental weight (D), Placental volume (E), Fetal weight (F) and Ratio FW/PW (G) values represented as a function of GA (12–41 weeks), with seven adjusted percentile curves (3rd, 10th, 25th, 50th, 75th, 90th and 97th).

without gender differentiation, and therefore, it was chosen not to categorize the curves by gender.

Selecting the most suitable data-fitting method was crucial to creating accurate growth curves. Based on the criteria detailed in Subsect. 2.2, the chosen methods were GAMLSS, LMS, LMST, and LMSP. These methods used P-splines, which are more computationally efficient than other smoothing functions, like cubic spiles [14]. Various distributions were tested using different methods for each placental parameter in the study. In the context of the D1, D2, R-FW and PV, the GAMLSS model with the BCT distribution was chosen to represent the percentile growth curve, due to its good performance. For the PT, PW and FW the LMST model was selected. This prominence is based on the high R^2 values and the reduction in errors, reflected in the relatively low values of MSE, AIC, and BIC. Furthermore, the analysis of the diagnostic plots and the agreement between the nominal and sample percentages confirmed the quality of this model.

These reference curves provide healthcare professionals with valuable tools to assess placental development clinically. By comparing placental parameters like D1 with the 3rd percentile curve for a given GA, it is possible to identify placental underdevelopment, crucial for the early detection of complications and monitoring maternal and fetal health. This methodology has broader applications and can be used to develop growth curves in various contexts. For more detailed information, see [35,42], which offers foundational guidance for future studies.

A significant challenge in this investigation was the scarcity of data and studies that allow for comparison and contextualization of the results of this investigation within the context of placental parameters. Over the years, reference percentile curves have been produced, mainly for FW in relation to GA, but these graphs are generally restricted to the third trimester of pregnancy and take into account specific cases such as fetal gender, parity, and ethnicity [16,29,46]. These conditions do not align with this study, as it explored various GA, including earlier stages such as 12 weeks, did not categorize by gender or parity, and only used data from the Portuguese population.

However, despite this lack of comparative data, some notable studies were identified that effectively explored placental parameters. One example is the study of [26] where the authors analyzed part of the dataset used in this investigation to construct growth curves for the placental parameters PW and FW. Comparing the percentile values and graphs, there are differences in the estimated values for each percentile at each GA and in the shape of the percentile curves. Since no metrics or diagnostic graphs are presented, it is not possible to compare the quality of fit with the curves of this study.

Another study that uses part of the dataset from this investigation is [21] where it was developed a percentile growth curve for the placental parameter D2 that is very similar to this study once it was used the same methodology.

The recent study of [16] demonstrates the successful use of the GAMLSS method to create reference curves related to PW, as they achieved a good quality

of fit. The results of this study clearly illustrate the effectiveness of the GAMLSS approach in analysing placental parameters, providing a valuable precedent for this work. However, since the study is done by categorizing by gender and parity for GAs between 28 and 42 weeks, no comparisons can be made with the curves developed in this investigation. Furthermore, the study by [8] is also relevant. This study played a fundamental role in the construction of the World Health Organization's child growth standards. The authors highlighted the feasibility of using GAMLSS, LMS, LMST, and LMSP models, due to their potential to produce promising results when age is treated as a continuous variable, similar to GA.

Therefore, although there is a lack of direct references, these cited studies demonstrate that the analysis of placental parameters, especially using methods such as GAMLSS, has the potential and capacity to produce significant results.

5 Conclusions

This study comprehensively explored placental parameters and their implications on maternal and fetal health, resulting in the development of reference growth curves for 12 to 41 weeks of gestation.

As contemporary challenges related to low birth rates and increasing maternal age are faced, promoting placental and fetal health becomes a fundamental priority. The developed percentile curves offer a detailed understanding of how the placental parameters D1, D2, PT, PW, PV, FW and R-FW evolve throughout pregnancy. Using GAMLSS and LMST models with P-splines and the BCT distribution proved effective for creating accurate reference curves. Specifically, the application of the GAMLSS method to model the D1, D2, R-FW and PV and the LMST method to model PT, PW and FW.

The scarcity of studies on placental biometric parameters, particularly for GAs between 12 and 41 weeks, for the Portuguese population, and the placental parameters in study, posed a significant challenge. However, the pioneering approach of this research fills a crucial gap in the literature, offering valuable information on placental growth patterns and their clinical significance. Despite the accomplishments, this work faces limitations and there are paths for future investigations. It is essential to continue refining methodologies and expanding study samples to enhance the applicability of placental reference growth curves.

For future work, a broader investigation could be conducted to improve the accuracy of the reference growth curves. Including more diverse samples of pregnant women, covering different ethnic groups, gestational ages, and medical conditions. Also, study the relationship of other variables with placental development, such as parity or maternal age, to understand if other factors influence placental parameters. However, the final goal of this research is to develop a web application to consolidate all the work done with the growth curves and make them accessible for easy and effective analysis.

Ultimately, this study reinforces the importance of investigating placental parameters and demonstrates how statistical and mathematical modelling can

lead to significant advancements in medicine. Despite the challenges faced, the results demonstrated the feasibility of the developed approach. It is hoped that this work will inspire future research and, at the same time, directly benefit the lives of pregnant women and their babies, promoting a healthy and safe pregnancy.

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