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Testing the assumptions of customized intrauterine growth charts using national birth studies

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Abstract

Introduction: Customized intrauterine growth charts are widely used for growth monitoring and research. They are based on three assumptions: (1) estimated fetal weight (EFW) has a normal distribution with a constant coefficient of variation at all gestational ages; (2) Hadlock’s growth curve accurately describes the relation between EFW and gestational ages; (3) associations between EFW and the fetal and maternal characteristics included in the customization model (fetal sex, pre-pregnancy weight, height, parity) are proportional throughout pregnancy. The aim of this study was to test whether these underlying assumptions are verified.

Material and methods: Data came from (1) the French Longitudinal Study of Children (ELFE) cohort, which recruited births after 32 weeks’ gestation in 349 maternity hospitals in France in 2011, and (2) the National Perinatal Survey, which included births from all French maternity hospitals in 2016. The study population included, respectively, 6,920 and 8,969 singleton non-malformed term live births with data on customization characteristics and EFW. We computed the coefficient of variation by gestational age and then modeled the association of gestational age, maternal and fetal characteristics with EFW at the second and third trimester ultrasound and with birthweight using linear regression. To assess the proportionality of the impact of maternal and fetal characteristics, we computed the percent change in weight associated with these characteristics at these three time points.

Results: The coefficient of variation was close to 12% at each gestational age, but EFW was not normally distributed, leading to small but systematic underestimation of fetuses under the 10th percentile. Weights representing the 50th and 10th percentiles based on Hadlock’s growth trajectory were lower than observed or predicted weights. Most characteristics more strongly impacted weight at birth than during pregnancy. In the French Longitudinal study of Children (ELFE) cohort, boys were 1.8% (95% confidence interval [CI] 1.3–2.4) heavier than girls in the third trimester,
Fetal growth restriction denotes the fetus’ failure to reach its full growth potential. It is associated with risks of stillbirth, neonatal death and neurodevelopmental impairment.\textsuperscript{1–3} When fetal growth restriction is detected during pregnancy, these risks can be reduced by close monitoring and early delivery.\textsuperscript{4–6} Therefore, intrauterine growth screening aims to identify fetuses at risk of fetal growth restriction, frequently defined as those with an estimated fetal weight (EFW) under the 10th percentile of a reference population.\textsuperscript{7–10}

Customized growth charts, proposed by Gardosi in the 1990s, aim to improve growth screening by differentiating between constitutionally small fetuses and those with suboptimal growth.\textsuperscript{11} They adjust for factors that physiologically affect birthweight, including maternal (pre-pregnancy weight, height, parity, ethnicity) and fetal (sex) factors.\textsuperscript{12–14} Customized charts are recommended in the UK, New Zealand and Ireland\textsuperscript{8} and were developed in France in 2015.\textsuperscript{15} Many studies have shown that taking into consideration these physiological factors identifies births with higher risks of adverse outcomes, such as stillbirth and neonatal death,\textsuperscript{16–18} although the model’s impact on population-level outcomes has been questioned.\textsuperscript{19}

Customized charts are based on modeling the impact of maternal and fetal characteristics on birthweight in a sample of normal pregnancies (singleton, live, non-malformed, term births).\textsuperscript{11} This model is used to calculate each fetus’ optimal birthweight at 40 weeks’ gestation; individualized norms are then derived for each gestational age (GA) by applying Hadlock’s growth trajectory formula,\textsuperscript{20} and percentiles are calculated using the coefficient of variation (CV) measured at 40 weeks’ GA. The model makes three key assumptions: (1) fetal weight is normally distributed with a constant CV, (2) Hadlock’s growth trajectory accurately describes fetal growth patterns, and (3) the effect of fetal and maternal characteristics is proportional throughout pregnancy, meaning that they increase fetal weight by the same percentage at all GA.\textsuperscript{11}

Despite the widespread use of customized models in research and clinical care, few studies have investigated these assumptions.\textsuperscript{21} Most evaluations of the model have been carried out using birthweight,\textsuperscript{16,17,22,23} but results may differ when the model is applied to EFW, used for screening. Indeed, recent comparisons with local or international charts based on EFW have shown no significant differences for the detection of adverse perinatal outcomes.\textsuperscript{24–26} The aim of this study was to test the three assumptions of the customized model using routine clinical data on EFW in the second and third trimesters of pregnancy.

## MATERIAL AND METHODS

### 2.1 Data sources

Data were sourced from two French population birth studies. By using two sources, we sought to assess the consistency and generalizability of study findings. The first source was the French Longitudinal Study of Children (ELFE) birth cohort, which recruited births from 349 maternity hospitals, randomly selected from 544 maternity hospitals in metropolitan France, over 25 days in 2011.\textsuperscript{27,28} Inclusion criteria were singleton or twin live births after 33 weeks’ gestation with mothers aged ≥18 years and parents understanding French, English, Arabic or Turkish who lived and planned to stay in France for at least 3 years and gave written informed consent (N = 18 329). The second source was the 2016 French National Perinatal Survey (NPS), which included all births with a GA of at least 22 weeks or a birthweight of at least 500 g during a 1-week period in 2016 in 517 maternity hospitals (N = 14 142).\textsuperscript{29} Stillbirths, births to minors and mothers refusing to participate in the full study only contributed partial data. For both studies, data were collected from medical records and an interview with mothers after delivery.

### 2.2 Variable selection and definition

Outcome variables were EFW at the second and third trimester routine ultrasound and birthweight. We also used GA at the ultrasounds.
and at birth in weeks and days. Second and third trimester ultrasounds are recommended in France for all pregnant women at 20–25 and 30–35 weeks' gestation, respectively, and it is also recommended that GA be calculated using crown–rump length measured before 14 weeks' gestation.

For the ELFE study, femur length and transverse abdominal diameter or – if the latter was not available – abdominal circumference ultrasound measures were collected from the second and third routine ultrasound reports in obstetrical records. We used Hadlock's formula based on abdominal circumference and femur length to calculate EFW since the value calculated at the ultrasound was not collected for this study. Information on transverse abdominal diameter was not used as this measure is no longer recommended for use in clinical practice, and there is no validated conversion formula for estimating abdominal circumference. The NPS collected data on EFW at the third trimester scan, as noted in medical records; biometric measurements and data on the second trimester scan were not collected in this study. We did not have information on the formula used to calculate EFW, but Hadlock's formula based on head circumference, femur length and abdominal circumference is recommended in France.

Our independent variables were those used in Gardosi's customized model: fetal sex, maternal height and pre-pregnancy weight, parity, GA and smoking in third trimester, with the exception of ethnicity, as these data are not collected routinely in France. As in Gardosi's methodology, the model is adjusted on smoking to include all pregnant women in the calculation of customization coefficients, without shifting weight distributions towards lower values due to maternal smoking. However, this characteristic is not used to predict optimal weight. Maternal age and educational level were used to describe and compare the samples but are not included in the customized model.

| TABLE 1 Demographic and clinical characteristics of the two samples |
|-----------------------|-----------------------|-----------------------|-----------------------|
|                       | ELFE cohort (N = 6 920) | NPS (N = 8 969) | p-value (χ² test or Student's test as appropriate) |
| Maternal age (years)  | 30.6 (5.0)            | 30.2 (5.1)         | <0.001               |
| Education level       |                       |                     |                       |
| Primary school        | 0.5                   | 0.9                 | <0.001               |
| Middle school         | 3.5                   | 5.9                 |                       |
| High school           | 34.7                  | 36.8                |                       |
| College               | 61.0                  | 56.0                |                       |
| Maternal weight before pregnancy (kg) | 63.9 (13.7) | 64.9 (14.1) | <0.001               |
| Maternal height (cm)  | 165.0 (6.2)           | 164.6 (6.3)         | <0.001               |
| Parity                |                       |                     |                       |
| 0                     | 45.8                  | 42.4                | <0.001               |
| 1                     | 35.0                  | 36.1                |                       |
| 2                     | 13.3                  | 14.3                |                       |
| 3                     | 4.2                   | 4.5                 |                       |
| 4 and more            | 1.8                   | 2.8                 |                       |
| Smoking status        |                       |                     |                       |
| Smoker                | 20.0                  | 15.2                | <0.001               |
| Fetal sex             |                       |                     |                       |
| Male                  | 51.6                  | 51.0                | 0.545                |
| Gestational age at 2nd trimester ultrasound (weeks) | 22.4 (0.9) | -- | -- |
| Estimated fetal weight at second trimester (g) | 538 (100) | -- | -- |
| Gestational age at third trimester ultrasound (weeks) | 32.5 (0.9) | 32.5 (0.9) | 0.062                |
| Estimated fetal weight at third trimester (g) | 2 010 (298) | 1 993 (282) | <0.001               |
| Gestational age at birth (weeks) | 39.8 (1.1) | 39.7 (1.1) | <0.001               |
| Birthweight (g)       | 3 371 (446)           | 3 334 (447)         | <0.001               |

Abbreviations: ELFE, étude longitudinale française depuis l'enfance (French Longitudinal Study of Children); NPS, National Perinatal Survey; SD, standard deviation.
2.3 Study population

We selected a sample of singleton non-malformed term live births, as used by Gardosi.11 After exclusion of births with minimal data (stillbirths and minors) and refusals in the NPS (n = 1,522), exclusions for multiples, congenital anomalies and preterm birth were 1,884 (ELFE) and 1,336 (NPS) (Supporting Information Figure S1). We excluded 942 and 274 women, respectively, for whom data on the variables for the customized model were missing. We then excluded women with ultrasounds done outside the recommended GA ranges (20–25 weeks in the second trimester and 30–35 weeks in the third trimester) in order to focus on routine ultrasounds only (n = 971 [ELFE]; 365 [NPS]).

We included women with data at all time points in order to evaluate the customized model during pregnancy and at birth using the same sample. All ultrasound data could be missing when ultrasound reports were not transcribed in medical records or because women did not have one or both of the ultrasounds (n = 3,470 [ELFE]; 968 [NPS]). This latter occurrence is infrequent as almost all women have these routine ultrasounds.29 Data could also be missing for one ultrasound parameter or for GA at ultrasound (n = 380 [ELFE]; 649 [NPS]). In the ELFE cohort, data were also missing when transverse abdominal diameter was collected without abdominal circumference (n = 3,762).

To verify the three assumptions underlying the customized model, we first compared the CV (standard deviation/mean) of EFW in the second and third trimesters and birthweight using the asymptotic test for the equality of CV by Feltz et al.35 The normality of the distribution of EFW and birthweight was tested using the Shapiro–Wilk test; we also calculated the percentages of fetuses and newborns with a weight under the 10th percentile when assuming a normal distribution.

Next, we estimated linear regression models for EFW at the second and third trimester ultrasound and birthweight, following the specifications used by Gardosi.11 In these models, continuous covariates were centered at their means. Maternal pre-pregnancy weight and GA were included in the model using a third-degree polynomial.

To compare growth trajectories,18 we plotted proportionality curves of Hadlock’s model expressed as a percentage of EFW.

2.4 Analysis strategy

First, we compared maternal and infant characteristics between the samples and between included and missing cases in each data source. To check the accuracy of our ultrasound data, we visually assessed concordance of EFW medians and 10th percentiles by GA with French College of Fetal Sonography references.34

Note: P-values of the test for the equality of the coefficients of variation equal 0.820 and 0.610 for ELFE and NPS, respectively.

**TABLE 2** Mean weight and coefficient of variation by gestational age at routine ultrasounds and at birth

| ELFE cohort (N = 6920) | National Perinatal Survey (N = 8,969) |
|------------------------|--------------------------------------|
| **Second trimester ultrasound** | |
| N | Mean weight | SD | CV (%) | 95% CI | N | Mean weight | SD | CV (%) | 95% CI |
| 20 | 172 | 391 | 64 | 16.5 | 14.8–18.2 | 302 | 1,635 | 202 | 12.4 | 11.4–13.3 |
| 21 | 1,310 | 456 | 56 | 12.2 | 11.7–12.7 | 1,614 | 1,815 | 214 | 11.8 | 11.4–12.2 |
| 22 | 3,620 | 527 | 62 | 11.7 | 11.4–12.0 | 4,772 | 1,977 | 234 | 11.8 | 11.6–12.1 |
| 23 | 1,361 | 603 | 78 | 12.9 | 12.4–13.4 | 1,772 | 2,139 | 243 | 11.4 | 11.0–11.7 |
| 24 | 362 | 708 | 112 | 15.9 | 14.7–17.0 | 352 | 2,360 | 277 | 11.7 | 10.9–12.6 |
| 25 | 95 | 815 | 143 | 17.6 | 15.1–20.1 |
| **Third trimester ultrasound** | |
| 30 | 246 | 1,635 | 209 | 12.8 | 11.6–13.9 | 302 | 1,635 | 202 | 12.4 | 11.4–13.3 |
| 31 | 1,242 | 1,820 | 221 | 12.1 | 11.7–12.6 | 1,614 | 1,815 | 214 | 11.8 | 11.4–12.2 |
| 32 | 3,383 | 1,987 | 247 | 12.4 | 12.1–12.7 | 4,772 | 1,977 | 234 | 11.8 | 11.6–12.1 |
| 33 | 1,550 | 2,152 | 262 | 12.2 | 11.7–12.6 | 1,772 | 2,139 | 243 | 11.4 | 11.0–11.7 |
| 34 | 370 | 2,340 | 306 | 13.1 | 12.1–14.0 | 352 | 2,360 | 277 | 11.7 | 10.9–12.6 |
| 35 | 129 | 2,508 | 326 | 13.0 | 11.4–14.6 | 157 | 2,544 | 301 | 11.8 | 10.5–13.1 |
| **At birth** | |
| 37 | 375 | 2,957 | 389 | 13.2 | 12.2–14.1 | 650 | 2,923 | 418 | 14.3 | 13.6–15.1 |
| 38 | 969 | 3,159 | 424 | 13.4 | 12.8–14.0 | 1,534 | 3,156 | 420 | 13.3 | 12.8–13.7 |
| 39 | 2,121 | 3,316 | 408 | 12.3 | 11.9–12.7 | 2,627 | 3,301 | 403 | 12.2 | 11.9–12.5 |
| 40 | 2,111 | 3,455 | 415 | 12.0 | 11.6–12.4 | 2,552 | 3,431 | 408 | 11.9 | 11.6–12.2 |
| 41 | 1,344 | 3,593 | 418 | 11.6 | 11.2–12.1 | 1,623 | 3,568 | 417 | 11.7 | 11.3–12.1 |

Note: P-values of the test for the equality of the coefficients of variation equal 0.820 and 0.610 for ELFE and NPS, respectively.

Abbreviations: CI, confidence interval; CV, coefficient of variation; ELFE, étude longitudinal française depuis l’enfance (French Longitudinal Study of Children); N/A, not applicable; NPS, National Perinatal Survey; SD, standard deviation.
calculated at 40 weeks’ gestation (3619 g) along with the 50th percentile of the predicted weights from our three models calibrated with all characteristics at their mean and the observed sample weights, both expressed as a percentage of mean birthweight at 40 complete weeks’ gestation as done in the customized model. We also plotted the 10th percentile computed by applying the observed CV at 40 weeks’ gestation to Hadlock’s model and to our models’ predicted weights, as specified by the customized model, as well as the 10th percentile observed from the data.

To test the final assumption that the associations of maternal and fetal characteristics with weight were similar throughout pregnancy, we computed the magnitude of the association as a percentage of the mean weight explained by each variable and its 95% confidence interval. This was calculated for each variable using the coefficients from the regression models, keeping other variables at their mean values. For example, the percentage impact of fetal sex was calculated as the ratio of the expected average weight of a boy over the expected average weight of a girl, from which we subtracted 1.

$$\text{Percentage impact}_{\text{gender}} = \frac{\sum \left[m_x \times k_x\right]}{\sum \left[0 \times k_x\right]} - 1$$

With $c$: model’s constant, $k$: model’s coefficient, $m$: mean, $a$ to $l$: other predictors.
For maternal weight and height, we calculated the percentage impact for a difference of 10 and 20 units from the mean (i.e. 65 kg and 165 cm, respectively). This value was calculated as a nonlinear combination of the estimated coefficients (formula nlcom in Stata 14.0). Analyses were conducted using complete cases; multiple imputation using chained equations with 100 imputed datasets was carried out as a sensitivity analyses.

**FIGURE 1** (Continued)

The x-axis corresponds to birthweight in grams and the y-axis corresponds to the density.

| GA | ELFE cohort (N = 6,920) | National Perinatal Survey (N = 8,969) |
|----|-------------------------|---------------------------------------|
|    | Histogram               | n  | p-value | %  | Histogram               | n  | p-value | %  |
| 37 |                         | 375| 0.74362 | 8.53 |                         | 650| 0.00022 | 9.41 |
| 38 |                         | 969| <0.00001 | 9.18 |                         | 1534| <0.00001 | 8.81 |
| 39 |                         | 2121| <0.00001 | 9.24 |                         | 2627| 0.00007 | 9.95 |
| 40 |                         | 2111| <0.00001 | 8.62 |                         | 2552| 0.04600 | 9.27 |
| 41 |                         | 1344| 0.00237 | 9.82 |                         | 1623| 0.00929 | 9.88 |

*P-values were computed using the Shapiro-Wilk test for normality.*
### TABLE 3  Modeling of estimated fetal weight at second and third trimester routine ultrasounds and birthweight with maternal and fetal characteristics

| Reference | Coefficient | SE | Coefficient | SE |
|-----------|-------------|----|-------------|----|
| **ELFE cohort** *(N = 6 920)* | | | **NPS** *(N = 8 969)* | | |
| **Model 1: EFW at second trimester** | | | | |
| GA | 11.0 | 0.2 | – | – |
| GA<sup>2</sup> | 0.1 | 0.02 | – | – |
| GA<sup>3</sup> | −0.001 | 0.001 | – | – |
| Fetal sex Female | 14.5 | 1.6 | – | – |
| Centered height 165 cm | 0.8 | 0.1 | – | – |
| Centered weight 65 kg | 0.2 | 0.01 | – | – |
| Centered weight<sup>2</sup> | −0.02 | 0.005 | – | – |
| Centered weight<sup>3</sup> | 0.0004 | 0.0001 | – | – |
| Parity 1 Parity 0 | 6.1 | 1.8 | – | – |
| Parity 2 | 3.2 | 2.5 | – | – |
| Parity 3 | 10.5 | 4.1 | – | – |
| Parity 4 | 14.9 | 6.1 | – | – |
| Smoking No | −0.9 | 2.0 | – | – |
| Constant | 492.5 | 1.8 | – | – |
| **Model 2: EFW at third trimester** | | | | |
| GA | 25.0 | 0.7 | 25.8 | 0.6 |
| GA<sup>2</sup> | 0.04 | 0.07 | 0.08 | 0.06 |
| GA<sup>3</sup> | 0.001 | 0.004 | −0.002 | 0.003 |
| Fetal sex Female | 36.8 | 5.8 | 45.7 | 4.7 |
| Centered height 165 cm | 1.8 | 0.5 | 2.2 | 0.4 |
| Centered weight 65 kg | 3.9 | 0.3 | 2.9 | 0.2 |
| Centered weight<sup>2</sup> | −0.07 | 0.02 | −0.07 | 0.01 |
| Centered weight<sup>3</sup> | 0.0009 | 0.0003 | 0.0007 | 0.0003 |
| Parity 1 Parity 0 | 35.5 | 6.5 | 10.9 | 5.3 |
| Parity 2 | 41.4 | 9.0 | 14.7 | 7.2 |
| Parity 3 | 51.8 | 14.8 | 36.2 | 11.8 |
| Parity 4 | −12.7 | 22.2 | 8.7 | 14.7 |
| Smoking No | −39.7 | 7.3 | −50.6 | 6.6 |
| Constant | 1 909.9 | 6.4 | 1 890.6 | 5.4 |
| **Model 3: Birthweight** | | | | |
| GA | 19.7 | 1.1 | 18.1 | 0.9 |
| GA<sup>2</sup> | −0.16 | 0.1 | −0.11 | 0.08 |
| GA<sup>3</sup> | 0.005 | 0.007 | 0.016 | 0.006 |
| Fetal sex Female | 151.1 | 9.3 | 140.6 | 8.0 |
| Centered height 165 cm | 7.1 | 0.8 | 7.5 | 0.7 |
| Centered weight 65 kg | 6.2 | 0.5 | 5.6 | 0.4 |
| Centered weight<sup>2</sup> | −0.19 | 0.03 | −0.13 | 0.02 |
| Centered weight<sup>3</sup> | 0.0020 | 0.0005 | 0.0013 | 0.0004 |
| Parity 1 Parity 0 | 111.5 | 10.4 | 118.5 | 9.1 |
| Parity 2 | 129.7 | 14.5 | 138.4 | 12.3 |
| Parity 3 | 145.6 | 23.7 | 135.1 | 20.1 |
| Parity 4 | 42.3 | 35.6 | 127.4 | 25.2 |
| Smoking No | −123.8 | 11.6 | −171.5 | 11.2 |
| Constant | 3 324.1 | 10.6 | 3 289.8 | 9.4 |

Abbreviations: EFW, estimated fetal weight; ELFE, étude longitudinale française depuis l'enfance (French longitudinal study of children); GA, gestational age; NPS, National Perinatal Survey; SE, standard error.
Ethical approval

The ELFE and NPS studies received ethical approval from relevant committees, including the French National Data Protection Authority (CNIL): N° 910504, March 17, 2011 (ELFE), and N° 915197, January 14, 2016 (NPS).

RESULTS

The study samples included 6,920 births from the ELFE cohort and 8,969 births from the NPS (Figure S1). Women in the ELFE cohort were slightly older, had lower average weight and higher average height than those in the NPS and were more often nulliparous, smokers and more educated (Table 1). Mean EFW and birthweight were slightly higher in the ELFE sample. In both studies, women with missing data had a lower educational level and higher EFW (Tables S1 and S2). In ELFE, women with missing data also delivered slightly earlier and had later third trimester ultrasound scans; those in the NPS were more often multiparous and smoked more. The median and 10th percentiles of EFW by GA were similar in both samples and concordant with French references (Figure S2).

Table 2 displays the mean weights and CV by GA. The CV were close to 12%, with higher variation for GA with fewer data points. The test for the equality of the CV with a null hypothesis that they were all equal and an alternative hypothesis that at least one was not equal to the others was not significant (p = 0.820 [ELFE] and 0.610 [NPS]). The EFW distribution was skewed towards lower values, and Shapiro–Wilk tests rejected the hypothesis of normality at almost all weeks of GA, which led to 5%–8% of fetuses with an EFW under the 10th percentile when assuming a normal distribution for all GA (Figures 1A–C).

Models of EFW at the second and third trimesters and of birthweight that included GA and maternal and fetal characteristics were computed (Table 3). Most coefficients did not differ by more than 25 g (corresponding to 25 g) between the two samples, except for parity 2 at second trimester (26.7) and for parity 4 and smoking at third trimester (85.1 and 47.7). They were first used to derive proportionality curves for the predicted 50th and 10th percentile weights for ELFE and NPS in comparison with Hadlock’s growth trajectories and observed percentiles, all expressed as a percentage of mean birthweight at 40 weeks’ gestation (Figure 2A–C). Results for ELFE and NPS were similar, with slightly higher observed than predicted values. These were both substantially higher than the expected values based on Hadlock’s trajectory from 20 weeks of gestation until 33 weeks of gestation.

As shown in Table 4, percentages of change in weight associated with characteristics were similar between the two samples, except for parity 1 in the second model and smoking status in the third model. Fetal sex and maternal height were associated with an increase in weight in all three periods, but the percentage of mean weight associated with these variables was higher at birth than at the third trimester ultrasound scan. Maternal weight before pregnancy and smoking status were associated with weight only in the third trimester and at birth. The percentage of mean weight associated with smoking status increased as the pregnancy progressed, whereas it was constant at the third trimester and at birth for maternal pre-pregnancy weight. The association of parity was significant starting in the second trimester in the ELFE cohort but only at birth in the National Perinatal Survey.

The percentage changes in weight were similar after multiple imputation (Table 5).

DISCUSSION

When applied to routine clinical EFW data, the customized model based on Hadlock’s growth trajectory differed from predicted and observed values at earlier GA, and the magnitude of the associations between EFW and fetal sex, maternal height and parity were less marked during pregnancy than at birth. CVs were similar across gestation, but EFW did not follow a normal distribution, leading to slight underestimation of the percentage of fetuses under the 10th percentile. These small but systematic errors raise questions about how...
this model performs when applied to EFW during antenatal growth screening as opposed to birthweight, which has been used for the majority of the evaluations of the model.16,17,22

The strengths of this study are the use of two large birth samples, confirming the consistency of the results. We assessed results at two time points during pregnancy with the ELFE sample, whereas the nationally representative design of the NPS provided estimates applicable to the French population. Limitations included missing EFW data when ultrasound reports were not available in obstetrical records; however, sensitivity analyses after imputation of missing data

| TABLE 4 Percent change in fetal weight and birthweight explained by maternal and fetal characteristics in the two samples |
|---------------------------------------------------------------|
| Reference | ELFE cohort (N = 6,920) | % | 95% CI | NP50 (N = 8,969) |
|-----------|-------------------------|---|---------|-----------------|
| **Model 1: EFW at second trimester** |
| 1 week gestation | 22 GA | 16.5 | 16.0–17.1 |
| Male | Female | 2.7 | 2.1–3.3 |
| Mean height + 10 cm | 165 cm | 1.5 | 1.0–2.0 |
| Mean height + 20 cm | 3.0 | 2.0–4.0 |
| Mean weight + 10 kg | 65 kg | 0.01 | −0.3–0.3 |
| Mean weight + 20 kg | −0.3 | −0.9–0.4 |
| Parity 1 | Parity 0 | 1.1 | 0.5–1.8 |
| Parity 2 | 0.6 | −0.3–1.5 |
| Parity 3 | 2.0 | 0.5–3.4 |
| Parity 4 | 2.9 | 0.5–5.0 |
| Smoker | Nonsmoker | −0.2 | −0.9–0.6 |
| **Model 2: EFW at third trimester** |
| 1 week gestation | 32 GA | 9.2 | 8.7–9.7 |
| Male | Female | 1.8 | 1.3–2.4 |
| Mean height + 10 cm | 165 cm | 0.9 | 0.4–1.4 |
| Mean height + 20 cm | 1.8 | 0.9–2.8 |
| Mean weight + 10 kg | 65 kg | 1.2 | 0.9–1.4 |
| Mean weight + 20 kg | 1.9 | 1.2–2.5 |
| Parity 1 | Parity 0 | 1.8 | 1.1–2.4 |
| Parity 2 | 2.1 | 1.2–3.0 |
| Parity 3 | 2.6 | 1.1–4.1 |
| Parity 4 | −0.6 | −2.8–1.5 |
| Smoker | Nonsmoker | −2.0 | −2.7 to −1.3 |
| **Model 3: Birthweight** |
| 1 week gestation | 40 GA | 3.9 | 3.5–4.3 |
| Male | Female | 4.6 | 4.0–5.2 |
| Mean height + 10 cm | 165 cm | 2.1 | 1.7–2.6 |
| Mean height + 20 cm | 4.2 | 3.3–5.2 |
| Mean weight + 10 kg | 65 kg | 1.3 | 1.0–1.6 |
| Mean weight + 20 kg | 1.9 | 1.3–2.5 |
| Parity 1 | Parity 0 | 3.4 | 2.7–4.0 |
| Parity 2 | 3.9 | 3.1–4.8 |
| Parity 3 | 4.4 | 3.0–5.8 |
| Parity 4 | 1.3 | −0.8–3.4 |
| Smoker | Nonsmoker | −3.6 | −4.3 to −3.0 |

Abbreviations: CI, confidence interval; EFW, estimated fetal weight; ELFE, étude longitudinale française depuis l’enfance (French Longitudinal Study of Children); GA, gestational age; NPS, National Perinatal Survey.
yielded similar results. In the ELFE sample, EFW was calculated using two biometric parameters; in the NPS sample, EFW was abstracted from the medical files without information on the formula, although Hadlock’s three parameter formula is recommended in France. Ultrasound measurements were collected retrospectively from clinical data and not a strict protocol, likely resulting in wider variability; nevertheless, this reflects the real-life conditions in which the model is applied. Measurement errors may bias results towards the null; however, reassuringly, the 50th and 10th percentiles were concordant with French ultrasound references. A final limitation is the absence of data

| Reference | ELFE cohort (N = 12 408) | NPS (N = 11 464) |
|-----------|--------------------------|------------------|
|           | % | 95% CI | % | 95% CI |
| Model 1 : EFW at second trimester | | | | |
| 1 week gestation | 22 GA | 16.7 | 16.1–17.2 | 17.8 | 17.0–18.6 |
| Male | Female | 2.3 | 1.7–2.9 | 2.1 | 1.5–2.7 |
| Mean height + 10 cm | 165 cm | 1.5 | 1.0–2.0 | 1.6 | 1.1–2.1 |
| Mean height + 20 cm | 3.0 | 2.0–4.0 | 3.2 | 2.2–4.2 |
| Mean weight + 10 kg | 65 kg | 0.3 | 0.0–0.6 | 0.4 | 0.1–0.7 |
| Mean weight + 20 kg | 0.3 | −0.3–1.0 | 0.4 | −0.2–1.0 |
| Parity 1 | Parity 0 | 0.9 | 0.3–1.5 | 0.8 | 0.2–1.4 |
| Parity 2 | 0.6 | −0.2–1.5 | 0.7 | −0.3–1.6 |
| Parity 3 | 2.1 | 0.6–3.5 | 2.2 | 0.7–3.7 |
| Parity 4 | 2.3 | 0.1–4.5 | 2.4 | 0.6–5.0 |
| Smoker | Nonsmoker | −0.4 | −1.1–0.4 | −0.4 | −1.1–0.4 |
| Model 2 : EFW at third trimester | | | | |
| 1 week gestation | 32 GA | 9.4 | 8.9–9.9 | 9.5 | 9.0–9.9 |
| Male | Female | 1.5 | 0.9–2.0 | 1.6 | 1.0–2.1 |
| Mean height + 10 cm | 165 cm | 0.8 | 0.3–1.3 | 0.9 | 0.4–1.4 |
| Mean height + 20 cm | 1.6 | 0.6–2.5 | 1.8 | 0.7–2.9 |
| Mean weight + 10 kg | 65 kg | 1.2 | 1.0–1.5 | 1.3 | 1.0–1.6 |
| Mean weight + 20 kg | 2.1 | 1.5–2.7 | 2.3 | 1.9–3.0 |
| Parity 1 | Parity 0 | 1.6 | 1.0–2.2 | 1.7 | 1.1–2.3 |
| Parity 2 | 1.6 | 0.8–2.5 | 1.8 | 0.9–2.9 |
| Parity 3 | 2.6 | 1.3–4.0 | 2.8 | 1.4–3.2 |
| Parity 4 | 0.3 | −1.8–2.5 | 0.5 | −0.9 to 1.7 |
| Smoker | Nonsmoker | −2.0 | −2.7 to −1.3 | −2.6 | −3.3 to −2.0 |
| Model 3 : Birthweight | | | | |
| 1 week gestation | 40 GA | 3.9 | 3.6–4.2 | 4.0 | 3.7–4.4 |
| Male | Female | 4.5 | 4.1–4.9 | 4.6 | 4.2–5.1 |
| Mean height + 10 cm | 165 cm | 2.1 | 1.8–2.5 | 2.3 | 1.9–2.7 |
| Mean height + 20 cm | 4.3 | 3.6–5.0 | 4.6 | 3.8–5.4 |
| Mean weight + 10 kg | 65 kg | 1.4 | 1.2–1.6 | 1.5 | 1.0–2.0 |
| Mean weight + 20 kg | 2.3 | 1.8–2.7 | 2.5 | 1.6–3.0 |
| Parity 1 | Parity 0 | 3.3 | 2.8–3.8 | 3.5 | 3.0–4.0 |
| Parity 2 | 3.8 | 3.1–4.4 | 4.1 | 3.4–4.9 |
| Parity 3 | 4.3 | 3.2–5.4 | 4.4 | 3.4–5.7 |
| Parity 4 | 1.9 | 0.3–3.5 | 2.1 | 1.4–3.9 |
| Smoker | Nonsmoker | −3.9 | −4.4 to −3.5 | −5.0 | −5.6 to −4.5 |

Abbreviations: CI, confidence interval; EFW, estimated fetal weight; ELFE, étude longitudinale française depuis l’enfance (French Longitudinal Study of Children); GA, gestational age; NPS, National Perinatal Survey.
on ethnicity, which are included in the customized model but were not collected in France.

The model's predicted fetal weights by GA were concordant between the two samples and close to observed values. However, they were not in line with Hadlock's trajectory used in the customized model, which predicted slightly lower mean and 10th percentile values for EFW. These results raise questions about whether Hadlock's growth trajectory, constructed from a sample of 392 women in the 1980s, describes fetal growth in France today. Differences were more pronounced for the 10th than for the 50th percentile. The CV in our sample was 12%, which is within the range reported in the literature and used in some models, but larger than the 11% used in Gardosi's model. The calculation of the 10th percentile also relies on the assumption of normality, which was not verified; statistical techniques to account for skewness could improve the model's fit.

The coefficients on maternal and fetal characteristics obtained in the birthweight models were similar for both samples and consistent with Gardosi's model, French customized charts and studies from other countries. One exception was the low coefficient for high parity (≥4) in ELFE, but few women were in this category. In contrast, we found an inconsistent association of fetal and maternal characteristics with EFW, with magnitudes generally less pronounced than at birth, as has been reported elsewhere for maternal height and body mass index.

Maternal pre-pregnancy weight and smoking had a larger impact at birth and the third trimester, and no association was observed in the second trimester. This could be explained by the extrinsic influence of these factors, which impact the environmental conditions of the fetus rather than growth potential itself. Considering the high prevalence of maternal smoking, the absence of an impact on EFW in the second trimester may lead to a slight overestimation of the model's predicted optimal weight. In contrast, fetal sex and maternal height had varying proportional impacts but were related to EFW starting in the second trimester. This may reflect the intrinsic genetic and biologic influence of these factors on fetal growth, supported by previous studies showing an impact starting in the first trimester.

Our results raise questions about how the customized model performs using ultrasound data. Most evaluations of the model have compared customized and unc customized charts using birthweight, but results may differ for EFW. In particular, our analyses raise questions about whether the model accurately describes the fetal growth trajectory and percentiles at all GA. This could impact on screening and lead to under-detection of fetuses at risk of fetal growth restriction if percentile values are too low. How the differences in the impact of maternal and fetal characteristics on EFW vs birthweight affect the model are less clear but highlight the need for research to assess and refine the customized model based on its performance when applied to EFW.

5 | CONCLUSION

This study raises questions about the validity of the assumptions underlying the customized growth model. Most importantly, our findings suggest that the modeled growth trajectory and, in particular, the modeled 10th percentile threshold may slightly, but systematically, underestimate true values, which would lead to under-detection of fetuses with growth restriction. Further evaluations of the performance of the customized growth model when applied to EFW are needed given the intended use of the customized charts for growth monitoring during pregnancy.

CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTIONS
AH and JZ had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: JZ, AH, IM, BH, BB, MND. Acquisition, analysis, or interpretation of data: JZ, AH, IM, BH, BB, MND. Drafting of the manuscript: AH, JZ. Critical revision of the manuscript for important intellectual content and approval of final version of the manuscript: JZ, AH, IM, BH, BB, NMD. Statistical analysis: JZ, AH, IM, BH.

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