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Prediction of the date of delivery based on first trimester ultrasound measurements: An independent method from estimated date of conception

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Abstract

Objective. We aimed to develop a population-based nomogram based on 1st trimester ultrasound examination as an independent predictor of the remaining days of pregnancy.

Methods. Fetal measurements were collected in singleton pregnancies undergoing first trimester examination. We prospectively collected actual date of delivery. Predictions of the median interval and key centiles from examination to delivery were computed using crown rump length (CRL), biparietal diameter (BPD), head circumference (HC), and abdominal circumference (AC) measurements.

Results. A total of 3738 examinations were included. We computed median and centiles for remaining days of pregnancies from the time of first trimester measurements. The prediction ability of CRL, HC, and BPD was not different but AC yielded worse results. About 90% of the births fell within 14 days of predicted day of delivery, with a median error of 6 days.

Conclusion. We have developed a method to accurately predict date of delivery from the time of first trimester measurements. It allows monitoring fetal growth and pregnancies at term by considering the duration of pregnancy as a variable rather than a constant.

Keywords: *First trimester, ultrasound, gestational age, pregnancy duration, quantile regression*

Introduction

Failure to achieve precise dating of pregnancy can result in iatrogenic prematurity or postmaturity, and both circumstances are associated with increased perinatal morbidity and mortality [1–3]. Most studies aim to predict the date of confinement and assume a standard duration of pregnancy with fixed thresholds for defining preterm and post-term pregnancies from an estimated date of conception. Gestational age has long been determined from the first day of the last menstrual period (LMP) based on the model of a regular 28-day menstrual cycle. However, the use of LMP is frequently hampered by memory bias [4] and even when LMP can be reliably recalled, various factors may delay ovulation and therefore cause inaccurate dating [5]. Conception occurring as a result of *in vitro* fertilization could reduce this imprecision because the time of conception is known, but these studies are based on very small samples [6]. Dating pregnancy by ultrasound (US) examination in the first and early second trimester of pregnancy using crown-rump length (CRL) and biparietal diameter (BPD) has proven more reliable than LMP-based methods to predict date of delivery within 5 days in up to 95% of cases [7–11]. However, US-based methods also aim at dating from date of conception.

There is evidence that duration of pregnancy should be considered as a continuous variable with

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more complications to be expected as pregnancy duration is more distant from its expected duration [1–3]. A new approach to pregnancy dating has emerged that aims to directly predict the remaining days of pregnancy based on US measurements in second or first trimester [12,13]. We aimed to develop new nomograms for predicting day of delivery based on a large sample of first trimester ultrasound measurements.

Material and methods

This study was conducted in an unselected population of singleton pregnancies undergoing first trimester ultrasound examination over the 2001–2006 period. Sonographic examination was part of our routine prenatal management policy and women gave oral informed consent prior to US examination in all cases. No IRB was sought because this research did not affect prenatal care. All measurements were performed to the mm with no time constrains using transabdominal US examination unless technical difficulty would indicate transvaginal US examination (3.5–5 and 7 Mhz probes, respectively, General Electric Voluson 730 Expert ultrasounds (GE Medical System Europe, 78530 Buc, France). Operators were experienced in prenatal ultrasound, performing more than 1000 prenatal examinations per year for over 10 years. Date of ultrasound examination, maternal age, CRL, BPD, head circumference (HC), and abdominal circumference (AC) together with outcomes of the pregnancies (i.e. day of delivery, live birth, termination, in utero fetal death, miscarriage) were prospectively collected in all cases. Freeze-frame, cine-loop facilities, and electronic on-screen callipers were used for measurements. CRL was measured to the nearest mm in a sagittal plane with the fetal head in a neutral position. BPD and HC were measured on a transverse view of the fetal head in a plane showing both thalami and the third ventricle. AC was measured on a transverse circular view of the fetal abdomen, just above the level of the cord insertion.

Fetuses with measurements between 35 and 90 mm, 12 and 30 mm, 35 and 110 mm, and 35 and 100 mm for CRL, BPD, HC and AC, respectively, were included in the study. Pregnancies with incomplete or abnormal outcome, multiple examinations or spontaneous or iatrogenic delivery below 35 weeks were excluded from the statistical analysis.

Time interval (T) in days between ultrasound examination and the day of delivery was regressed on each predictor (X) (i.e. CRL, BPD, HC, and AC) using quantile regression models [14], a fully parametric approach that estimates the conditional quantile distribution of T given $X = x$ by the minimization of the absolute residuals. In particular, we estimated the median and the 1st, 3rd, 5th, 10th, 90th, 95th, 97th, and 99th centiles. To evaluate possible non-linear relationships between the remaining days of pregnancy and first trimester ultrasound measurements, we compared the linear model with more complex models containing restricted cubic splines of the predictor [15]. Within these regression models, the user specified k knots located at specific values of the predictor $m_1, m_2, \ldots m_k$. Variables were then created to model a continuous smooth function (f) that is linear before m_1, a piecewise cubic polynomial between adjacent knots, and again linear after m_k [16]. This method enables for a flexible relationship between response and predictor, where the level of smoothness is controlled by the number of the specified knots. The knots in the spline models were placed at equally spaced centiles.

A validation procedure was used to choose the most appropriate number of splines knots, to compare the fitting of both linear and non-linear models, as well as to assess the reproducibility of the estimates. The approach consisted of a 50-fold cross-validation of the random sample estimates. The random sample was first randomly divided in 50 subsets of approximately equal size. The outcome in each group was then predicted by a fitted model using data from the other subsets, and the process was repeated for every group. To compare the fit of the different predictors and the form of the relationship, we evaluated the size and the distribution of the absolute residuals obtained by cross-validation and the proportion of births falling within ± 7 and ± 14 days of predicted date of birth. A sensitivity analysis was carried out to check the fit of the models, considering the size of the residuals in different regions of predictors' distribution. Multivariable models with two or more different US measurements were also tested to assess if prediction accuracy could be gained.

All statistical analyses were performed using Stata 9.2 for Windows (StataCorp LP, TX). Basic variables for the spline transformations were obtained using *rc_spline* Stata command. Quantile regression models were generated using the *qreg* command, specifying the particular centile required to be estimated.

Results

A total of 3738 examinations met the inclusion criteria during the study period. Complete first trimester measurements were available in all but 80 and 33 cases for AC and HC, respectively. Table I shows the summary statistics of our population.

Cross-validation analysis identified the 1-knot spline transformation as the most appropriate for all ultrasound measurements. From here on we referred to it as the 'non-linear median model'. When compared with the linear one, a more precise estimate of the remaining time of pregnancy was observed for all predictors. As an example, Table II illustrates the difference between linear and non-linear models for CRL.

The prediction ability of CRL, HC, and BPD was not different but AC yielded worse results (Table III). Table III shows a comparison of the distribution of absolute residuals from non-linear quantile regression model based on the four different ultrasound measurements at first trimester. About 90% of the births fell within ± 14 days of predicted day of delivery, with a median error of ~5.9 days (Table III). Models with more than one predictor did not perform better than univariable models and corresponding results are therefore not showed.

Tables IV–VII give median and key centiles for the remaining time to delivery according to measurements between 40 and 90 mm, 15 and 30 mm, 45 and 105 mm, and 35 and 90 mm for CRL, BPD, HC and AC, respectively, as obtained from non-linear univariable models.

Corresponding predictions are illustrated in Figures 1–4 for CRL, BPD, HC and AC, respectively.

Discussion

Gestational age assessment by ultrasound is the corner stone of modern obstetrics [17]. This is the first study providing with median and key centiles for the remaining days of pregnancy based on first trimester measurements. It differs from all previous studies as it predicts the remaining days from first trimester ultrasound to delivery directly without the need to estimate the date of conception and, therefore, not using gestational age.

Only one study used a comparable approach [12]. However, Gjessing et al. used less accurate second trimester measurements and performed a local linear quantile regression (semi-parametric method). Second trimester measurements have proven less accurate than first trimester measurement at dating pregnancies [18]. Our method allows early planning of pregnancy management and early reassurance to the mother [19]. The use of routine fetal nuchal translucency (NT) screening for Down syndrome has resulted in most pregnancies being examined and dated at 11–14 weeks [20]. Saltvedt et al. [18] reported a smaller random error at early dating, supporting the hypothesis that early dating yields more precise estimates of gestational age than late dating. This is in agreement with smaller biological variation of fetal size in early pregnancy and Taipale and Hiilesmaa [21] found that the prediction error in GA estimates to be lowest at 12–14 weeks' gestation. At earlier gestation, Taipale and Hiilesmaa [21] found crown-rump length measurement of 15–60 mm to be the best determinant, whereas BPD (at least 21 mm) was more precise thereafter. Accuracy was not improved when any two or all ultrasound variables were included in prediction models, confirming previous observations that combining informations from more than one adequately obtained ultrasound measurement in estimating the day of the delivery is not effective [17,21].

The models developed are based on the actual observed day of delivery. This is a more reliable indicator than the estimated day of LMP that

Table I. Summary statistics of the main variables.

	N	Mean	Std. dev.	Min	Max
Time interval between US and delivery	3738	190.7	9.9	153	218
Maternal age (years)	3735	30.3	4.3	18.1	47.0
Crown rump length (mm)	3738	63.6	8.2	40	90
Biparietal diameter (mm)	3738	21.8	2.7	15	30
Head circumference (mm)	3705	78.3	9.3	45	105
Abdominal circumference (mm)	3658	62.0	7.9	35	90

Table II. Comparison of prediction ability based on CRL by cross-validation: distribution of absolute residuals.

Model	*N*	Mean	Median	Inter quartile range	% in ± 7 days	% in ± 14 days
Linear median	3738	7.05	5.99	6.68	57.8	90.6
Nonlinear median (spline)	3738	7.05	5.87	6.72	57.9	90.7

Table III. Comparison of prediction ability based on different ultrasound measurements at first trimester: distribution of absolute residuals from non-linear quantile regression model.

Predictors	Obs	Mean	Median	Inter quartile range	% in ± 7 days	% in ± 14 days
Crown rump length (mm)	3738	7.05	5.87	6.72	57.9	90.7
Biparietal diameter (mm)	3738	7.08	5.85	6.90	59.3	90.1
Head circumference (mm)	3705	7.11	5.85	6.73	59.3	89.9
Abdominal circumference (mm)	3658	7.09	5.86	6.90	59.0	89.7

Table IV. Key quantiles for the predicted remaining days based on CRL measurements.

CRL	1st	3rd	05th	10th	50th	90th	95th	97th	99th
40	167.3	176.6	183.9	191.4	205.0	213.9	214.5	215.0	217.2
41	167.2	176.3	183.5	190.9	204.4	213.3	214.0	214.5	216.7
42	167.1	176.1	183.1	190.3	203.8	212.8	213.5	214.1	216.2
43	166.9	175.8	182.6	189.7	203.2	212.2	213.0	213.6	215.7
44	166.8	175.6	182.2	189.2	202.6	211.6	212.5	213.1	215.2
45	166.7	175.3	181.7	188.6	202.0	211.1	212.0	212.7	214.6
46	166.5	175.1	181.3	188.0	201.5	210.5	211.5	212.2	214.1
47	166.4	174.8	180.9	187.5	200.9	210.0	211.0	211.8	213.6
48	166.3	174.6	180.4	186.9	200.3	209.4	210.5	211.3	213.1
49	166.1	174.3	180.0	186.4	199.7	208.9	210.0	210.8	212.6
50	166.0	174.1	179.6	185.8	199.1	208.3	209.5	210.4	212.1
51	165.9	173.8	179.1	185.2	198.5	207.8	209.0	209.9	211.5
52	165.7	173.6	178.7	184.7	197.9	207.2	208.5	209.4	211.0
53	165.6	173.3	178.3	184.1	197.3	206.7	208.0	209.0	210.5
54	165.5	173.1	177.8	183.6	196.8	206.1	207.5	208.5	210.0
55	165.3	172.8	177.4	183.0	196.2	205.6	207.0	208.1	209.5
56	165.2	172.6	177.0	182.4	195.6	205.0	206.5	207.6	209.0
57	165.0	172.3	176.5	181.9	195.0	204.5	206.0	207.1	208.5
58	164.9	172.1	176.1	181.4	194.4	203.9	205.5	206.7	208.0
59	164.7	171.8	175.7	180.8	193.9	203.4	205.0	206.2	207.5
60	164.5	171.5	175.2	180.3	193.3	202.8	204.5	205.7	207.0
61	164.3	171.2	174.8	179.8	192.8	202.3	204.0	205.3	206.5
62	164.0	170.8	174.4	179.3	192.3	201.8	203.6	204.8	206.1
63	163.7	170.5	173.9	178.9	191.7	201.3	203.1	204.4	205.6
64	163.4	170.1	173.5	178.4	191.3	200.8	202.6	203.9	205.2
65	163.1	169.7	173.1	178.0	190.8	200.3	202.2	203.4	204.8
66	162.7	169.3	172.7	177.6	190.3	199.9	201.7	203.0	204.4
67	162.3	168.9	172.3	177.2	189.9	199.4	201.3	202.5	204.0
68	161.9	168.4	171.8	176.9	189.4	198.9	200.9	202.0	203.7
69	161.4	168.0	171.4	176.5	189.0	198.5	200.4	201.6	203.3
70	161.0	167.5	171.0	176.2	188.6	198.1	200.0	201.1	203.0
71	160.5	167.0	170.6	175.8	188.2	197.6	199.6	200.7	202.7
72	160.0	166.5	170.2	175.5	187.8	197.2	199.2	200.2	202.3
73	159.5	166.0	169.8	175.2	187.4	196.8	198.7	199.7	202.0
74	159.0	165.5	169.4	174.9	187.0	196.4	198.3	199.3	201.7
75	158.5	165.0	169.0	174.6	186.6	195.9	197.9	198.8	201.4
76	158.0	164.5	168.5	174.3	186.2	195.5	197.5	198.4	201.1
77	157.5	164.0	168.1	173.9	185.8	195.1	197.1	197.9	200.7
78	157.0	163.5	167.7	173.6	185.4	194.7	196.6	197.4	200.4
79	156.5	163.0	167.3	173.3	185.0	194.2	196.2	197.0	200.1
80	156.0	162.5	166.9	173.0	184.6	193.8	195.8	196.5	199.8
81	155.5	162.0	166.5	172.7	184.2	193.4	195.4	196.1	199.5
82	155.0	161.5	166.1	172.4	183.8	193.0	195.0	195.6	199.1
83	154.5	161.0	165.7	172.1	183.4	192.5	194.5	195.1	198.8
84	154.0	160.5	165.3	171.7	183.0	192.1	194.1	194.7	198.5
85	153.5	160.0	164.8	171.4	182.6	191.7	193.7	194.2	198.2
86	153.0	159.5	164.4	171.1	182.2	191.3	193.3	193.8	197.8
87	152.5	159.0	164.0	170.8	181.8	190.8	192.9	193.3	197.5
88	152.0	158.5	163.6	170.5	181.4	190.4	192.4	192.8	197.2
89	151.5	158.0	163.2	170.2	181.0	190.0	192.0	192.4	196.9
90	151.0	157.5	162.8	169.9	180.6	189.6	191.6	191.9	196.6

women may not accurately remember [4] or than the estimated day of conception which remains hypothetical even when derived from US measurements. The predictions that we have developed are completely independent from LMP and from gestational age and are derived from a large population-based registry of women scanned at first trimester. The main drawback of previous GA-based methods is that they can provide an estimate of the predicted day of delivery, but not of the uncertainty of this estimate. Indeed, they introduce an additional error by assuming a total length of pregnancy of 280 days, whereas pregnancy duration is a variable and not a constant [18]. The standard error of GA based models only includes the part of uncertainty related to the day of confinement for the prediction of the day of delivery. Saltvedt et al. suggested that the standard deviation (SD) of 'normal' pregnancy

Table V. Key quantiles for the predicted remaining days based on BPD measurements.

BPD	1st	3rd	05th	10th	50th	90th	95th	97th	99th
15	167.5	176.1	182.0	187.3	203.9	212.8	214.6	215.3	216.7
16	167.0	175.2	180.8	186.0	202.0	211.0	212.7	213.5	215.0
17	166.5	174.4	179.6	184.7	200.1	209.2	210.9	211.7	213.2
18	166.0	173.6	178.4	183.4	198.2	207.4	209.0	209.9	211.5
19	165.5	172.7	177.1	182.1	196.4	205.6	207.1	208.1	209.7
20	164.9	171.9	175.9	180.8	194.5	203.9	205.3	206.4	208.1
21	164.2	170.9	174.7	179.5	192.8	202.3	203.7	204.8	206.5
22	163.2	169.8	173.6	178.3	191.2	200.8	202.3	203.5	205.3
23	162.0	168.5	172.4	177.2	189.9	199.4	201.2	202.5	204.3
24	160.6	167.0	171.3	176.1	188.6	198.2	200.3	201.7	203.5
25	159.0	165.5	170.2	175.1	187.5	197.1	199.5	201.0	202.9
26	157.5	164.0	169.1	174.0	186.4	196.0	198.7	200.3	202.2
27	155.9	162.5	168.0	172.9	185.2	194.9	197.9	199.7	201.6
28	154.3	161.0	167.0	171.9	184.1	193.8	197.1	199.0	201.0
29	152.8	159.4	165.9	170.8	183.0	192.7	196.4	198.4	200.4
30	151.2	157.9	164.8	169.8	181.9	191.6	195.6	197.7	199.8

Table VI. Key quantiles for the predicted remaining days based on HC measurements.

HC	1st	3rd	05th	10th	50th	90th	95th	97th	99th
45	170.1	174.3	180.1	186.3	208.6	217.7	218.3	218.7	222.8
47	169.7	174.0	179.7	185.8	207.6	216.7	217.3	217.8	221.8
49	169.3	173.8	179.4	185.4	206.5	215.6	216.4	216.9	220.7
51	168.9	173.6	179.1	185.0	205.5	214.6	215.4	216.0	219.6
53	168.5	173.4	178.7	184.6	204.4	213.5	214.5	215.1	218.5
55	168.0	173.2	178.4	184.2	203.4	212.5	213.5	214.2	217.5
57	167.6	172.9	178.0	183.8	202.3	211.4	212.6	213.3	216.4
59	167.2	172.7	177.7	183.4	201.3	210.4	211.6	212.4	215.3
61	166.8	172.5	177.3	183.0	200.2	209.3	210.7	211.5	214.2
63	166.4	172.3	177.0	182.6	199.2	208.3	209.7	210.5	213.2
65	166.0	172.1	176.6	182.2	198.1	207.3	208.7	209.6	212.1
67	165.5	171.8	176.3	181.8	197.1	206.2	207.8	208.7	211.0
69	165.1	171.6	176.0	181.4	196.1	205.2	206.8	207.8	209.9
71	164.7	171.3	175.6	180.9	195.0	204.2	205.9	207.0	208.9
73	164.2	171.0	175.2	180.5	194.0	203.2	205.0	206.1	207.9
75	163.7	170.7	174.8	180.0	193.0	202.2	204.1	205.3	207.0
77	163.2	170.2	174.3	179.5	192.1	201.3	203.3	204.5	206.2
79	162.6	169.7	173.8	179.0	191.2	200.5	202.5	203.7	205.4
81	162.0	169.0	173.2	178.4	190.3	199.8	201.8	203.0	204.8
83	161.3	168.3	172.6	177.7	189.5	199.1	201.2	202.3	204.3
85	160.6	167.5	172.0	177.1	188.8	198.4	200.6	201.7	203.9
87	159.9	166.6	171.3	176.4	188.0	197.8	200.0	201.1	203.5
89	159.1	165.7	170.6	175.6	187.3	197.2	199.5	200.5	203.1
91	158.4	164.8	169.9	174.9	186.6	196.7	198.9	199.9	202.8
93	157.6	163.9	169.1	174.2	185.8	196.1	198.4	199.3	202.5
95	156.8	163.0	168.4	173.5	185.1	195.5	197.8	198.7	202.1
97	156.1	162.1	167.7	172.8	184.4	194.9	197.3	198.1	201.8
99	155.3	161.2	167.0	172.1	183.7	194.4	196.7	197.6	201.5
101	154.6	160.3	166.3	171.3	182.9	193.8	196.2	197.0	201.1
103	153.8	159.4	165.6	170.6	182.2	193.2	195.6	196.4	200.8
105	153.0	158.5	164.9	169.9	181.5	192.7	195.1	195.8	200.4

duration in singletons is about 8 days. Thus, in an ultrasound unit with perfect dating scans the SD of pregnancy duration as calculated from ultrasound fetometry should be ~ 8 days when including only singletons with spontaneous onset of labor at ≥ 37 weeks. This is in perfect agreement with the distribution of our residuals. By using the median, our term predictions are not influenced by post-term inductions which could thus be included in the analysis, neither by skewed distributions induced by preterm deliveries. Any mean-based prediction would however be influenced by such distribution components. Our method allows estimating the day of delivery and an interval of prediction. It allows

Table VII. Key quantiles for the predicted remaining days based on AC measurements.

AC	1st	3rd	05th	10th	50th	90th	95th	97th	99th
35.0	170.5	180.6	183.9	190.4	208.8	216.6	217.8	219.3	220.6
37.0	170.0	179.8	183.2	189.5	207.4	215.4	216.6	218.2	219.5
39.0	169.4	179.0	182.5	188.7	206.1	214.2	215.5	217.0	218.4
41.0	168.9	178.2	181.7	187.8	204.8	213.0	214.3	215.8	217.3
43.0	168.3	177.5	181.0	186.9	203.4	211.8	213.2	214.6	216.2
45.0	167.8	176.7	180.2	186.0	202.1	210.6	212.0	213.5	215.1
47.0	167.2	175.9	179.5	185.2	200.7	209.4	210.8	212.3	214.0
49.0	166.7	175.1	178.7	184.3	199.4	208.2	209.7	211.1	212.9
51.0	166.1	174.4	178.0	183.4	198.1	207.0	208.5	209.9	211.8
53.0	165.6	173.6	177.2	182.6	196.7	205.8	207.3	208.7	210.6
55.0	165.0	172.8	176.5	181.7	195.4	204.6	206.2	207.6	209.5
57.0	164.4	172.0	175.7	180.8	194.1	203.5	205.1	206.4	208.5
59.0	163.8	171.2	174.9	180.0	192.9	202.4	204.0	205.4	207.5
61.0	163.1	170.4	174.1	179.1	191.7	201.3	203.0	204.4	206.5
63.0	162.4	169.6	173.3	178.3	190.7	200.4	202.2	203.5	205.7
65.0	161.5	168.7	172.4	177.5	189.8	199.6	201.4	202.7	204.9
67.0	160.7	167.9	171.5	176.7	189.0	198.8	200.7	201.9	204.2
69.0	159.7	167.0	170.5	175.9	188.2	198.1	200.0	201.3	203.6
71.0	158.8	166.1	169.6	175.1	187.5	197.4	199.4	200.6	203.0
73.0	157.9	165.2	168.6	174.3	186.8	196.7	198.8	200.0	202.4
75.0	156.9	164.3	167.7	173.5	186.1	196.0	198.2	199.4	201.8
77.0	156.0	163.4	166.8	172.7	185.4	195.3	197.6	198.8	201.2
79.0	155.0	162.6	165.8	172.0	184.6	194.7	197.1	198.1	200.6
81.0	154.0	161.7	164.9	171.2	183.9	194.0	196.5	197.5	200.0
83.0	153.1	160.8	163.9	170.4	183.2	193.3	195.9	196.9	199.4
85.0	152.1	159.9	163.0	169.6	182.5	192.6	195.3	196.3	198.8
87.0	151.2	159.0	162.0	168.8	181.8	191.9	194.7	195.6	198.2
89.0	150.2	158.1	161.1	168.0	181.1	191.3	194.1	195.0	197.6
90.0	149.8	157.7	160.6	167.6	180.7	190.9	193.8	194.7	197.3

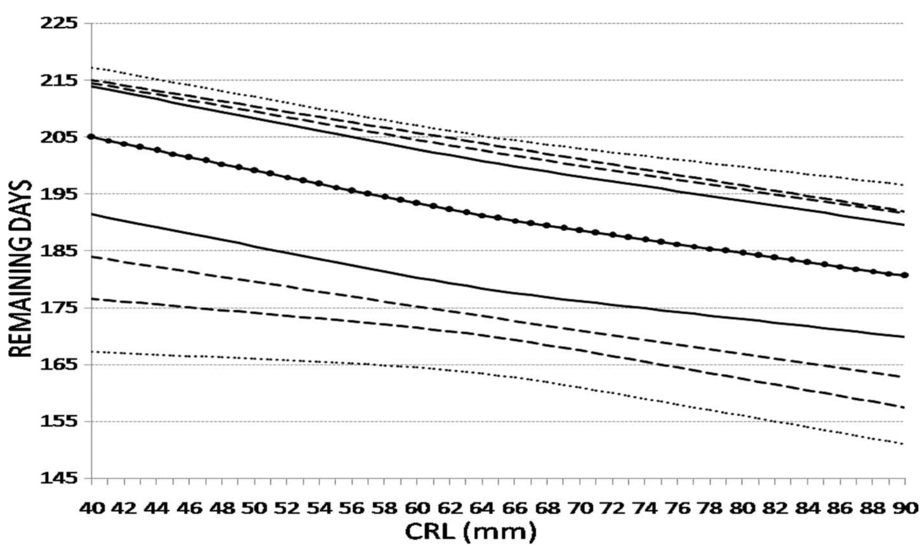

Figure 1. Prediction of 1st, 3rd, 5th, 10th, median, 90th, 95th, 97th, and 99th centiles remaining days to delivery based on CRL by spline quantile regression model.

estimating the different centiles without any distributional assumption (e.g. normality) of gestational age at delivery. As highlighted by Altman and Chitty, although fetal dimensions have a close to normal distribution at each GA, the reverse is not true [22]. For each fetal size, the distribution of remaining days of gestation is skewed because of preterm deliveries, and normality assumptions would be severely violated and inference about parameters highly biased, especially confidence intervals, if classical methods were to be used.

The method we have used is different from Gjessing' et al. [12], who performed a local linear quantile regression, consisting in a semi-parametric

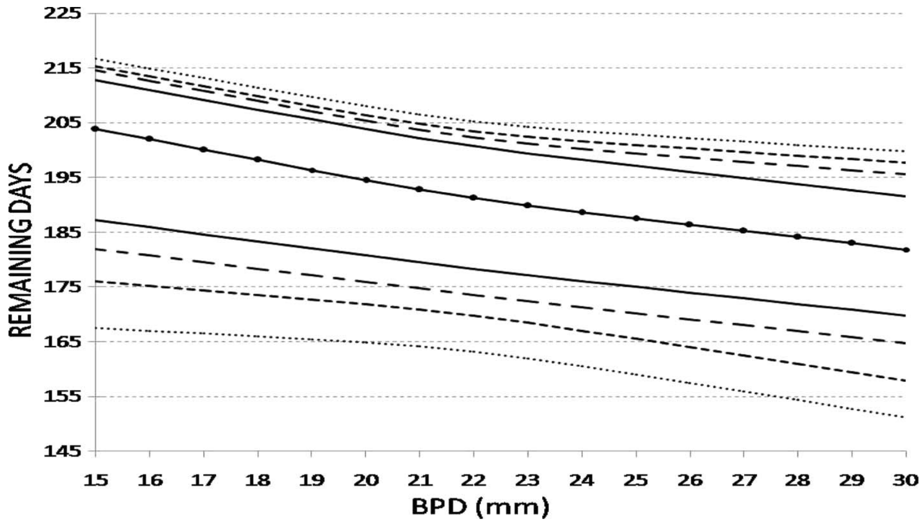

Figure 2. Prediction of 1st, 3rd, 5th, 10th, median, 90th, 95th, 97th, and 99th centiles remaining days to delivery based on BPD by spline quantile regression model.

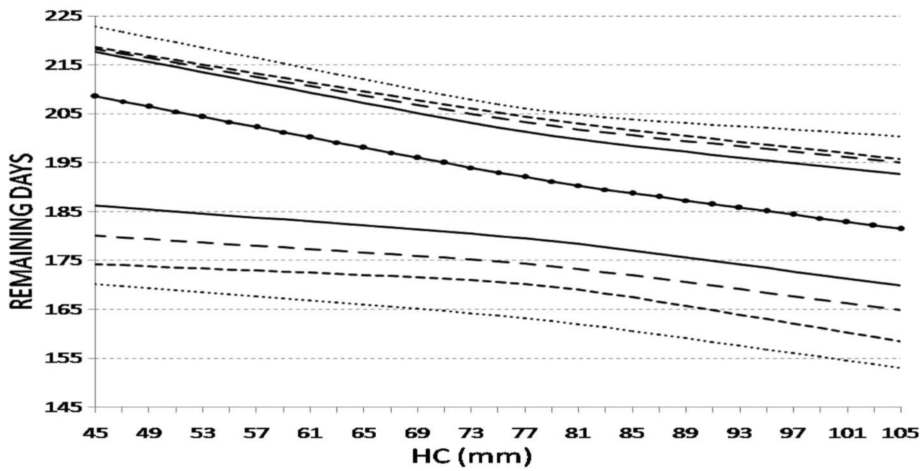

Figure 3. Prediction of 1st, 3rd, 5th, 10th, median, 90th, 95th, 97th, and 99th centiles remaining days to delivery based on HC by spline quantile regression model.

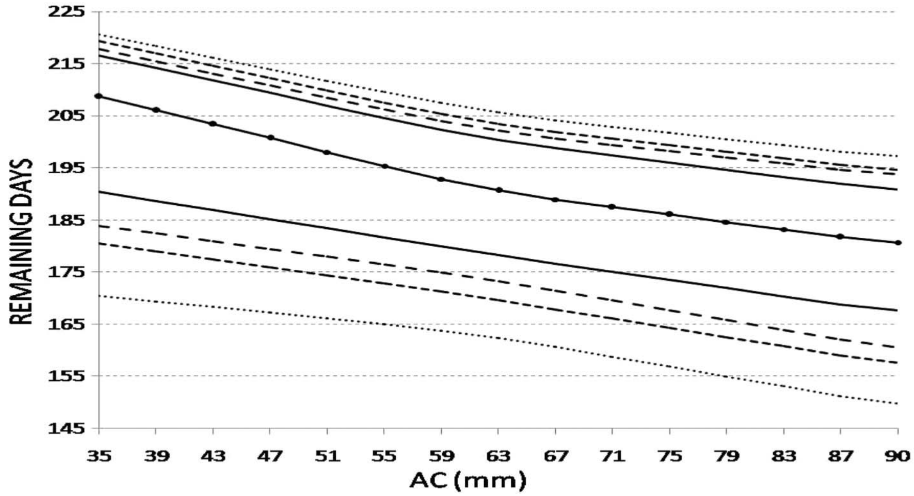

Figure 4. Prediction of 1st, 3rd, 5th, 10th, median, 90th, 95th, 97th, and 99th centiles remaining days to delivery based on AC by spline quantile regression model.

method based on a series of linear regressions. They did not provide with means allowing to compute centiles of the remaining time in pregnancy [12]. Our non-linear quantile model is flexible and does not rely on specific distributional assumptions. The level of smoothness can be controlled by the number of knots and it can easily be implemented with usual statistical software. We also used a validation procedure that prevents the model to be too constrained or over-fitted because of local random variations, it provides an estimate of the ability to predict outcomes in 'new cases' arising from the same population. The main limitation of our model is that it cannot provide with exact confidence intervals for the predictions, but only with estimates of various percentiles of the distribution. These estimates are affected by errors that cannot be taken into account when we predict the interval for a new pregnancy. However, the large population studied makes this error very small when compared with the residual variance and the approximation is therefore negligible. Another limitation of our approach is the absence of statistical tests to compare our models (linear-nonlinear, number of knots). However, choices were based on cross-validation methods which directly evaluate the prediction ability of the different models.

Our method allows to consider the duration of pregnancy as a continuous variable, establishing median and key centiles. Consideration of most variables in medicine and particularly in obstetrics has evolved from a fixed threshold to a continuous variable with a risk of adverse outcome changing with the measurement. Key examples include growth restricted fetuses which have long been considered small if weighing less than a certain weight [23,24], NT which was considered abnormal when above 3 mm before being considered as a continuous predictor of abnormalities [20]. It is likely that the same will apply to the duration of pregnancy and our results should allow further studies to investigate perinatal morbidity and mortality in relation to quantiles of gestational age at delivery.

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L. J. Salomon designed the study, supervised the analysis and wrote most the manuscript. J. P. Bernard co-designed the study and supervised its realization as well as the manuscript. A. Gasparini and C. Pizzi performed the statistical analysis. Y. Ville supervised the study and the manuscript writing. Women gave oral informed consent prior to ultrasound examination (US) in all cases. There was no IRB because this research did not modify routine prenatal care.

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